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Health and Environmental Effects Profile for Bromochloromethanes

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16. ABSTRACT

The Health and Environmental Effects Profile for bromochloromethanes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for the class as a whole.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value for the class as a whole.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR BROMOCHLOROMETHANES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AFC	Antibody forming cells
BCF	Bioconcentration factor
$\overline{bw}$	Body weight
cGMP/cAMP	Cyclic guanidine monophosphate/cyclic adenosine monophosphate
CNS	Central nervous system
CS	Composite score
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ED_{10}	Effective dose to 10% of the recipients
GC/MS	Gas chromatography/mass sepctrometry
GOT	Glutamic oxalacetic transaminase
K_{oc}	Soil sorption coefficient
K_{oh}	Reaction rate constant for OH radical
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion

LIST OF ABBREVIATIONS (cont.)

RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The structures, CAS Registry numbers, molecular weights and empirical formulas of the bromochloromethanes are presented in Table 1-1.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The physical properties of the bromochloromethanes are listed in Table 1-2. In general, the bromochloromethanes are sparingly soluble in water but miscible or soluble in many organic solvents such as alcohols, ethers, or benzene (Hawley, 1977; Weast, 1980).

1.3. PRODUCTION DATA

The only production volume data provided were available from the EPA TSCA Production File for 1977; these data are listed in Table 1-3. SRI (1984) lists Dow Chemical (Midland, MI) as a current manufacturer of bromochloromethane and Olin Corp. (Rochester, NY) as a current manufacturer of bromotrichloromethane. In addition, Dow Chemical produced bromotrichloromethane and Olin produced bromochloromethane in 1983 (USITC, 1984). In 1983, Dow and Olin produced >5000 lbs or $5000 worth of bromotrichloromethane while Dow and Buckman Laboratories produced >5000 lbs or $5000 worth of bromochloromethane (USITC, 1984). There are no available data that indicate that bromodichloro-, dibromochloro-, dibromodichloro- or tribromochloromethane are manufactured in the United States on an industrial scale. Pertinent data regarding the importation of bromochloromethanes were not located in the available literature ited in the Appendix.

Bromochloromethane is prepared by partial replacement of chloride in dichloromethane by reaction with anydrous $AlBr_3$, treatment with Br_2 and Al, or by reaction with HB_r followed by water washing and distillation

TABLE 1-1

Structures, CAS Registry Numbers, Molecular Weights and Empirical Formulas of Bromochloromethanes

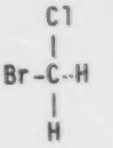
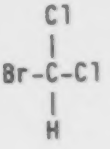
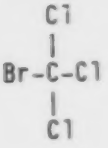
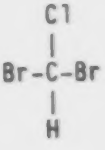
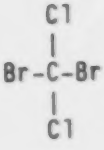
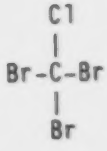
Bromochloromethanes	CAS Number	Molecular Weight	Empirical Formula	Structure
Bromochloromethane	74-97-5	129.39	CH_2BrCl	
Bromodichloromethane	75-27-4	163.83	$CHBrCl_2$	
Bromotrichloromethane	75-62-7	198.28	$CBrCl_3$	
Dibromochloromethane	124-48-1	208.29	$CHBr_2Cl$	
Dibromodichloromethane	594-18-3	242.74	CBr_2Cl_2	
Tribromochloromethane	594-15-0	287.19	CBr_3Cl	

TABLE 1-2

Physical Properties of the Bromochloromethanes[a]

Property	Bromochloromethane	Bromodi-chloromethane	Bromotri-chloromethane	Dibromo-chloromethane	Dibromodi-chloromethane	Tribromo-chloromethane
Melting point, °C	-86.5	-57.1	-5.6	NA	38	55
Boiling point, °C (1 atm)	68.1	90	104.7	119-20 (748 mm Hg)	150.2	158-9
Specific gravity, 20/4°C	1.9344	1.980	2.0122	2.451	NA	2.71 (15°C)
Refractive index, 20°C	1.4838	1.4964	1.5063	1.5482	NA	NA
Vapor Pressure, mm Hg	93.34 at 15.71°C[b] 141.07 at 24.05°C	50 at 20°C[c]	31.5 at 20°C[b]	15 at 10.5°C[c]	NA	NA
Water solubility	0.9 g/100 g at 25°C[d] 0.129 M at 25°C[f]	3032 ppm at 30°C[e]	NA	1050 ppm at 30°C[e]	NA	NA
Log octanol/water partition coefficient	1.41[f]	1.88 (calculated)[c]	NA	2.09 (calculated)[c]	NA	NA
Physical appearance at room temperature	colorless, volatile liquid with a chloroform-like odor[g]	liquid	colorless, heavy liquid with chloroform-like odor[g]	colorless, heavy liquid[g]	solid	leaflets
Henry's Law Constant at 25°C, atm-m³/mol	NA	0.00212[h]	NA	0.000783[h]	NA	NA

[a]Source: Weast, 1980 (unless otherwise noted)

[b]Kudchadker et al., 1979

[c]Callahan et al., 1979

[d]Stenger, 1978

[e]McNally and Grob, 1983

[f]Wasik et al., 1981

[g]Hawley, 1977

[h]Shen, 1982

NA = Not available

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TABLE 1-3

Bromochloromethane Production Data from TSCA Production File*

Bromochloromethanes	Producer	Production Volume (lbs)
Bromochloromethane	Dow Chemical Buckman Laboratories	1-10 million 10-100 thousand
Bromodichloromethane	Columbia Organic Chem. Plant Site Confidential	<1000 1-10 thousand
Bromotrichloromethane	Velsicol Chem. Rohm and Haas Co. (importer)	NR none
Dibromochloromethane	Columbia Organics	<1000
Dibromodichloromethane	none	none
Tribromochloromethane	none	none

*Source: U.S. EPA, 1980a

NR = Not reported

(Stenger, 1978). The vapor-phase bromination of chloroform can be used to prepare bromotrichloro-, dibromodichloro- and chlorotribromomethane (DeShon, 1979).

Bromochloromethanes (such as bromodichloro- and dibromochloromethane) have been inadvertently formed during drinking water and wastewater chlorination processes under appropriate conditions (Section 2.1.).

1.4. USE DATA

Bromochloromethane is primarily used as a fire-extinguishing fluid, particularly in aircraft and portable extinguishers (Stenger, 1978). It is also is used in organic syntheses (Hawley, 1977). Bromotrichloromethane is used in organic syntheses (Hawley, 1977) and as a chain-transfer agent in the polymerization of bromotrifluoroethylene (Astrologes, 1980). Bromodichloromethane is used in fire-extinguishing fluids, solvents (fats, waxes, resins), organic syntheses and mineral-salt separations (Stenger, 1978; Verschueren, 1983). Dibromochloromethane has potential use in fire-extinguishing agents, the manufacture of aerosol propellants and refrigerants, and syntheses of organics and pesticides (Verschueren, 1983). Pertinent data regarding uses for other bromochloromethanes were not located in the available literature cited in the Appendix.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The environmental fate of bromochloromethanes depends upon their ability to undergo chemical, photochemical and biological alterations and to transport or partition from one environmental matrix (air, water, soil-sediment) into another.

2.1. WATER

Mabey and Mill (1978) reported maximum hydrolytic half-lives and first order hydrolysis rate constants for bromochloromethanes at pH 7 and 25°C (Table 2-1). These rates indicate that hydrolysis of the listed bromochloromethanes is not environmentally significant. Hydrolysis data for the remaining bromochloromethanes were not located in the available literature cited in the Appendix; however, the chemical structure suggests that environmental hydrolysis is not important for these compounds as well.

Data pertaining specifically to the rate of photolysis of bromochloromethanes under environmentally significant conditions in the aquatic media were not located in the available literature cited in the Appendix. Ogita et al. (1983) reported that bromodichloromethane and dibromochloromethane, in aqueous solution at room temperature, are decomposed by UV irradiation of $\geq$200 nm. Hautecloque (1963) and Sidebottom et al. (1969) reported that bromotrichloromethane in the gaseous-phase at temperatures >122°C is decomposed to CCl_4 and C_2Cl_6 when exposed to Hg vapor radiation at 365 nm. UV spectra, as determined by Cadman and Simons (1966), predict that direct photolysis of bromochloromethane and bromodichloromethane has no significance in the environment; however, photolysis of bromotrichloromethane may be significant because it adsorbs UV radiation >290 nm. Therefore, additional data are needed in order to determine whether photolysis plays a significant role in removing bromochloromethanes from the aquatic environment.

TABLE 2-1

Maximum Hydrolytic Half-Lives and First-Order Hydrolysis Rate Constants for Bromochloromethanes[a,b]

Bromochloromethanes	Half-Life (years)	Rate Constant
Bromochloromethane	44	5.0×10^{-10} sec^{-1}
Bromodichloromethane	137	1.6×10^{-10} sec^{-1}
Dibromochloromethane	274	0.8×10^{-10} sec^{-1}

[a]Source: Mabey and Mill, 1978

[b]At pH 7 and 25°C

Data regarding the rate of oxidation of bromochloromethanes in the aquatic media were not located in the available literature cited in the Appendix. Bromodichloromethane and dibromochloromethane are similar to halogenated aliphatics in that they are not easily oxidized in aquatic systems because there are no functional groups that react strongly with hydroxyl radicals (Callahan et al., 1979).

Bouwer et al. (1981) tested the biodegradability of bromodichloromethane and dibromochloromethane under aerobic and anaerobic conditions with mixed methanogenic bacterial cultures from primary sewage effluents. The results of the anaerobic tests, which were conducted in the dark at 35°C, are summarized in Table 2-2. In the bacterial cultures, both bromochloromethanes were totally degraded within 2 weeks; however, in the sterile controls, degradation was also noted suggesting a chemical removal mechanism. The anaerobic results indicate, however, that the bacterial removal mechanism predominates. The aerobic degradation experiments, conducted at concentrations ranging from 12-85 ppb, produced no degradation in either the controls or seeded cultures. Bouwer and McCarty (1983a) examined the degradation of bromodichloromethane and dibromochloromethane under methanogenic conditions in batch bacterial cultures and in a continuous-flow methanogenic fixed-film laboratory-scale column. Using initial concentrations of 12-37 ppb, Bouwer and McCarty (1983a) found rapid degradation in the seeded cultures and slow degradation in the controls. These results were consistent with those of Bouwer et al. (1981). Bouwer and McCarty (1983a) suggested that biotransformation of bromodichloro- and dibromochloromethane can occur under methanogenic conditions in the environment. Bouwer and McCarty (1983b) studied the transformation of bromodichloro- and dibromochloromethane under anoxic conditions and in the presence of denitrifying bacteria. Control (sterile)

TABLE 2-2

Anaerobic Degradation of Bromodichloromethane and Dibromochloromethane in the Presence of Methanogenic Bacteria[a]

Week	High Concentration (ppb)	Medium Concentration (ppb)	Low Concentration (ppb)
Bromodichloromethane			
Controls			
0	161	35	16
6	69	16	8
16	46	18	3
Seeded Cultures			
2	<0.1[b]	<0.1	<0.1
Dibromochloromethane			
Controls			
0	205	45	19
6	65	8	7
12	33	11	1
Seeded Cultures			
2	<0.1	<0.1	<0.1

[a]Source: Bouwer et al., 1981

[b]Detection limit

tests conducted under the batch denitrification conditions produced no transformations of the bromochloromethanes after an 8-week period; however, degradation >50% was noted in the bacterial cultures after 8 weeks. Bouwer and McCarty (1983b) suggested that biotransformation in the environment is likely to occur under denitrification conditions.

Tabak et al. (1981) studied the biodegradability of 114 organic priority pollutants included on the U.S. EPA Priority Pollutants list to ascertain the extent of microbial degradation and acclimation periods. The Bunch and Chambers static culture flask biodegradability screening test was performed under a set of controlled experimental conditions that included the following: 5 and 10 mg/ℓ concentrations of the test compound, 5 mg/ℓ of yeast extract as a synthetic medium, a 7-day static incubation of 25°C in the dark, followed by three weekly subcultures (totaling 28 days of incubation), and incorporating settled domestic wastewater as microbial inoculum. The results of these tests with respect to bromochloro-, bromodichloro- and dibromochloromethane are listed in Table 2-3. The results suggest that bromochloromethane exhibits significant biodegradation, bromodichloromethane shows intermediate biodegradability, while dibromochloromethane exhibits recalcitrance towards biodegradation.

Patterson and Kodukala (1981) reported that a patented DuPont process (involving activated sludge with powdered activated carbon added) is >99% efficient in removing bromochloromethane and dibromochloromethane from influent waters containing 54 and 81 ppb of each chemical, respectively.

In a groundwater recharge field experiment, Rittman et al. (1980) injected water containing low concentrations of bromodichloromethane into a well located 10 m from an observation well. The time of travel from injection well to observation well was ~0.75 days. Bromodichloromethane passed through the biologically active zone with no appreciable degradation.

TABLE 2-3

Biodegradability and Volatility Studies with Bromochloromethanes Evaluated by the Static-Screening-Flask Test Method*

Compound	Concentration (mg/L)	Average Total Percent Loss of Test Compound in 7 Days Incubation Time (5)				Percent Volatilization Loss (5)		Performance Summary
		Origin Culture	First Subculture	Second Subculture	Third Subculture	5°C	25°C	
Bromochloromethane	5	100	100	100	100	0	11	D
	10	100	100	100	100	0	3	D
Bromodichloromethane	5	35	54	56	59	0	8	A
	10	34	44	46	51	0	1	A
Dibromochloromethane	5	25	28	35	39	0	16	N
	10	10	12	21	25	0	3	N

*Source: Tabak et al., 1981

D = Significant degradation with rapid adaption

A = Significant degradation with gradual adaption

N = Not significantly degraded under the condition of test method and/or precluded by extensive rate of volatilization

Bromodichloromethane and dibromochloromethane (as well as tribromomethane and trichloromethane) have been identified as being present in widespread samples of chlorinated drinking waters and in other waters subjected to chlorination processes and that their presence is a result of formation of these compounds during the chlorination process (Symons et al., 1975; Veenstra and Schnoor, 1980; Brett and Calverley, 1979; Glaze and Rawley, 1979; Arguello et al., 1979; Otson et al., 1982; Hollod and Wilde, 1982; Otson et al., 1981; Thomason et al., 1978; Gould et al., 1983; Cooper et al., 1983a,b; Hartwig and Valentine, 1983; Norwood et al., 1983; Trussell et al., 1980; Glaze et al., 1980; Oliver, 1980; Minear and Bird, 1980; Claeys et al., 1980; Bean et al., 1980; Rook, 1977; Stevens et al., 1976; Morris and McKay, 1975; Trussell and Umphres, 1978; Dore et al., 1982). The amount of trihalomethanes produced during these chlorination processes depends upon a variety of parameters, which include temperature, pH, bromide ion concentration of the water, fulvic and humic substance concentration of the water and chlorination treatment practices.

Rook (1977) and Trussell and Umphres (1978) suggested that bromodichloromethane (and other trihalomethanes) is formed during water chlorination treatments by a haloform reaction. This reaction requires an organic precursor, such as fulvic acid and humic substances that are present in many surface waters. The chlorination treatment process produces hypochlorous acid (HOCl) and ClO^- ions in the water. Bromide ion present in natural waters is oxidized to hypobromous acid (HOBr) by these aqueous chlorination products. The HOBr and HOCl then react with the organic precursors to form bromodichloromethane, dibromochloromethane, tribromomethane and trichloromethane (Dore et al., 1982). The yield of bromodichloro- and dibromochloromethane produced by aqueous chlorination treatment is low (Rook, 1977) and

varies with changes in conditions. Typical concentrations of bromodichloro- and dibromochloromethane found in chlorinated drinking water range from 0-50 ppb (Section 3.1.).

The transport of the bromochloromethanes in the aquatic media depends upon the ability of the compounds to volatilize, to adsorb to particulate matter in the water, or to bioaccumulate in aquatic organisms.

Kaczmar et al. (1984) experimentally measured the gas transfer rate constants of oxygen and bromodichloro- and dibromochloromethane under laboratory conditions and used these rate constants to calculate aquatic half-life volatilization ranges for each compound. The ratio of the gas transfer rate constants remained relatively constant over a wide range of temperature (3.8-25.3°C) and turbulent conditions. Using the experimentally measured gas transfer ratios and published values of environmental oxygen re-aeration rate constants for ponds, rivers and lakes of various characteristics, the following volatilization half-lives were calculated:

bromodichloromethane	33 minutes - 12 days
dibromochloromethane	43 minutes - 16.6 days

These estimated half-life ranges suggest that volatilization is an important mechanism for the removal of these two bromochloromethanes from the aquatic environment.

Rapid evaporation rates of bromodichloro- and dibromochloromethane from aqueous solution were also experimentally measured by Francois et al. (1979). The evaporation mechanism was found to be first-order at 25°C with initial aqueous concentrations of 8.7 and 20.7 µg/ℓ of bromodichloromethane and dibromochloromethane, respectively. Using the experimentally

derived rate constants, evaporation half-lives for bromodichloromethane and dibromochloromethane were calculated to be 58.2 and 61.9 minutes, respectively.

Using available water solubility and vapor pressure data for bromochloromethane (see Table 1-2), the Henry's Law Constant is estimated (calculated) to be 0.0014 atm-m^3/mol. This value suggests that volatilization of bromochloromethane from the aquatic environment is both rapid and significant. It is likely that bromochloromethane will volatilize from a water solution more rapidly than either bromodichloromethane or dibromochloromethane.

Rook (1974) reported that while flowing through open channels the concentration of bromodichloromethane and dibromochloromethane decreases as a result of volatilization. Also, Tabak et al. (1981) noted volatilization losses of bromochloro-, bromodichloro- and dibromochloromethane during biodegradation studies (see Table 2-3).

Data presented in Section 2.3. predict that the bromochloromethanes have a medium-to-high soil mobility and are therefore, not tightly bound to soil through adsorption. Therefore, it is likely that adsorption and subsequent precipitation of bromochloromethane in sediments does not compete with volatilization in the disappearance of bromochloromethane from the aquatic environment.

No measured steady-state BCF was found for any of the bromochloromethanes. BCF values can be estimated from correlation equations by using water solubility and log k_{ow} data.

From the three correlation equations listed below, estimated BCFs can be calculated for bromochloromethane, bromodichloromethane and dibromochloromethane (Table 2-4).

$$\text{Log BCF} = 2.791 - 0.564 \text{ Log WS} \quad \text{(Kenaga and Goring, 1978)} \qquad (2\text{-}1)$$

$$\text{Log BCF} = 0.76 \text{ Log } K_{ow} - 0.23 \quad \text{(Veith et al., 1980)} \qquad (2\text{-}2)$$

$$\text{Log BCF} = 0.935 \text{ Log } K_{ow} - 1.495 \quad \text{(Kenaga and Goring, 1978)} \qquad (2\text{-}3)$$

where: WS = water solubility in ppm (see Table 1-2)
K_{ow} = octanol-water partition coefficent (see Table 1-2)

These values suggest that bromochloromethanes are not likely to bioaccumulate in aquatic organisms to significant levels.

2.2. AIR

The atmospheric chemical removal processes include reaction of the target chemical with different free radicals (OH•, O•, Cl•, etc.), with ozone, or photolytic transformations. Rate constants for the reaction of the bromochloromethanes with OH radicals or with ozone are not available. Rate constants are available, however, for chloro-, dichloro-, trichloro- and bromomethane (Lyman et al., 1982); K_{OH} is on the order of magnitude of 10^{10} cm^3/mol-sec. Therefore, assuming that the rate constants for bromochloromethanes are near the same order of magnitude, atmospheric residence times can be calculated to be <2 years, which is not a significant removal mechanism.

TABLE 2-4

BCF Estimations for Bromochloromethanes

Compounds with Calculated BCF Values	Equation 2-1	Equation 2-2	Equation 2-3
Bromochloromethane	3.6	6.9	0.7
Bromodichloromethane	6.7	15.8	1.8
Dibromochloromethane	12.2	22.8	2.9

UV spectra, as determined by Cadman and Simons (1966), predict that direct photolysis of bromochloromethane and bromodichloromethane has no significance in the air environment because neither shows absorption of UV radiation >275 nm. Bromotrichloromethane, however, shows an absorption minimum of ~300 nm. Hautecloque (1963) and Sidebottom et al. (1969) reported that bromotrichloromethane in the gaseous-phase at temperatures above 122°C is decomposed to CCl_4 and C_2Cl_6 when exposed to Hg vapor radiation at 365 nm. Young (1959) has shown that bromotrichloromethane is readily photolyzed with radiation of 253.7 nm (which is not environmentally important). The significance of photolysis in the removal of bromochloromethanes from the atmosphere cannot be ascertained without additional investigation.

The physical removal processes, which include dissolution, adsorption on aerosol particles and dry deposition, are not likely to be significant with respect to bromochloromethanes.

2.3. SOIL

Microbial degradation data presented in Section 2.1. indicate that various bromochloromethanes can be decomposed biologically under certain environmental aquatic conditions. Wilson et al. (1983) found that bromodichloromethane is degraded slowly in soil obtained from below the water table (1.2-5.0 m depth). Also, Kobayashi and Rittman (1982) reported that bromochloro- and dibromochloromethane can be attacked by soil bacteria under anaerobic-anoxic conditions. Therefore, the microbial degradation of bromochloromethanes in the soil may be important, but the degree of importance cannot be ascertained without additional data.

Data regarding the chemical hydrolysis and surface photolysis of bromochloromethanes in the soil were not located in the available literature cited in the Appendix.

Wilson et al. (1981) used a laboratory soil column test to study the transport and fate of bromodichloromethane in a sandy soil. The soil had the following characteristics: sand, 92%; silt, 5.9%; clay, 2.1%; organic content, 0.087%; and pH 6.4. The columns received 14 cm of water/day, which resulted in unsaturated flow through almost the entire length of the column. Surface concentrations of 0.18 and 0.82 mg/ℓ bromodichloromethane were applied to the column. Volatilization, transport, and apparent degradation were monitored. Approximately 50% of the applied bromodichloromethane volatilized from the soil column; the remainder was transported through the column with no apparent degradation. Therefore, bromodichloromethane is expected to have significant mobility, particularly in sandy soils.

The equations listed below have been used to estimate K_{oc} values for bromochloromethane, bromodichloromethane, and dibromochloromethane from water solubility values and other physical properties (Table 2-5).

$$\text{Log } K_{oc} = 3.64-0.55 \text{ Log WS (Kenaga and Goring, 1978)} \quad (2-4)$$

$$\text{Log } K_{oc} = 1.377+0.544 \text{ Log } K_{ow} \text{ (Kenaga and Goring, 1978)} \quad (2-5)$$

$$\text{Log } K_{oc} = -0.54 \text{ Log WS mole fraction (Karickhoff et al., 1979)} \quad (2-6)$$

where: WS = water solubility in ppm

These calculated K_{oc} values indicate that the bromochloromethanes have a medium-to-high soil mobility. Therefore, it is possible that leaching may transport bromochloromethanes from soil into underlying groundwaters. The characteristics of the soil will determine the degree of importance of the leaching mechanism.

TABLE 2-5

K_{oc} Estimations for Bromochloromethanes

Compound	Equation 2-4	Equation 2-5	Equation 2-6
Bromochloromethane	29	139	37
Bromodichloromethane	53	251	75
Dibromochloromethane	95	327	468

Volatilization from soil is an important transport process of the bromochloromethanes, as indicated by the previously cited data of Wilson et al. (1981). In dry soils, volatilization is likely to be the predominant environmental fate process due to the high vapor pressures of bromochloromethanes. In moist soils, volatilization will still be important, but will occur in combination with leaching and, perhaps, an uncertain amount of microbial degradation.

3. EXPOSURE

3.1. WATER

As noted in Section 2.1., bromodichloromethane and dibromochloromethane have been identified in widespread samples of chlorinated drinking water and in other waters subjected to chlorination processes, and their presence is a result of formation during the chlorination treatment. Numerous papers and documents are available from the literature that have identified bromo-, dichloro- and dibromochloromethane in drinking waters and in other waters; however, the scope of this report limits use of data to the literature that is indicative of the widespread exposure.

In the National Organics Reconnaissance Survey (NORS), the U.S. EPA analyzed the raw water sources and the finished waters of 80 United States cities for the presence of bromodichloromethane, dibromochloromethane, and other trihalomethanes and chlorohydrocarbons (Symons et al., 1975). Table 3-1 summarizes the results with respect to bromodichloro- and dibromochloromethane and shows that while these compounds were frequently found (90% or more of the time) in finished waters, they were rarely detected in the raw water supplies (0-8.75% of the time). Symons et al. (1975) concluded that the presence of bromochloromethanes resulted from the chlorination treatments.

In its Region V Organics Survey of 83 sites of drinking waters, the U.S. EPA reported 78% of the locations had positive results for bromodichloromethane with a median concentration of 0.006 mg/ℓ and a maximum concentration of 0.031 mg/ℓ (U.S. EPA, 1975; Morris and McKay, 1975). Additionally, dibromochloromethane was found in 60% of the locations with median and maximum concentrations of 0.001 and 0.015 mg/ℓ, respectively.

TABLE 3-1

Bromodichloromethane and Dibromochloromethane Analysis
in the National Organics Reconnaissance Survey of 80 Cities*

Bromochloromethanes	Number of Cities with Positive Detections	Concentration (mg/ℓ)		
		Minimum	Maximum	Median
Bromodichloromethane				
Raw Water Source	7	<0.0002	0.0008	NR
Finished Water	78	0.0003	0.116	0.006
Dibromochloromethane				
Raw Water Source	0	NA	NA	NA
Finished Water	72	0.0004	0.110	0.0012

*Source: Symons et al., 1975

NR = Not reported; NA = Not applicable

The U.S. EPA National Organic Monitoring Survey (NOMS), which was conducted in three phases during 1976 and 1977, sampled 113 public water supplies representing various sources and treatments for specific organic compounds (Brass et al., 1977). The frequency of occurrence and concentration of bromochloromethane and dibromochloromethane are summarized in Table 3-2. In addition, bromochloromethanes were detected in various other potable waters (U.S. EPA, 1980b).

Data from a Canadian national survey for halomethanes in drinking waters are in general agreement with data from the United States (Health and Welfare Can., 1977). Samples taken from 70 finished water distribution systems showed bromodichloro- and dibromochloromethane in the following concentrations in µg/ℓ:

	Range	Median
bromodichloromethane	0-33	1.4
dibromochloromethane	0-6.2	0.1

Trussell et al. (1980) surveyed drinking waters from 12 areas of the world (southern China, Taiwan, Philippines- north and south, Egypt, Indonesia, Australia, England, Brazil, Nicaragua, Venezuela and Peru) for the presence of bromodichloro- and dibromochloromethane. Bromodichloromethane was found in 9 of the 12 waters at levels ranging from 1.7-10 µg/ℓ while dibromochloromethane was found in 7 waters at levels ranging from 1.1-13 µg/ℓ.

During 1981 and 1982, the U.S. EPA, Office of Drinking Water, Technical Support Division, Cincinnati, OH, conducted a sampling and analysis program of finished waters that use groundwater sources (Westrick et al., 1984). A total of 945 random and nonrandom water supplies were measured for bromo-, dichloro- and dibromochloromethane and other volatile organic compounds.

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TABLE 3-2

Frequency of Occurrence and Concentrations of Bromochloromethane and Dibromochloromethane in a Three-Phase Survey of 113 Water Supplies[a,b]

Bromochloromethanes	Sample	Number of Positive Analyses per Number of Analyses			Mean Concentration mg/ℓ (positive results only)			Mean Concentrations mg/ℓ (all results)		
		Phase			Phase			Phase		
		I	II	III	I	II	III	I	II	III
Bromodichloromethane	Q[c]	88/111[d]	18/18	100/106	0.022[d]	0.016	0.0092	0.0096	0.018	0.0059
	T[e]		109/113	103/105		0.018	0.017		0.014	0.011
Dibromochloromethane	Q[c]	47/111[f]	15/18	83/106	0.017[d]	0.013	0.0075	0.0006-0.003[f]	0.0019	0.0021
	T[e]		97/113	97/105		0.014	0.011		0.0035	0.0031

[a]Source: U.S. EPA, 1978

[b]Phases (I, II, III) refer to sampling projects and corresponding sample treatment and storage conditions.
I: Collected and analyzed as in National Organics Reconnaissance Survey (earlier) (Symons et al., 1975). Shipped and stored refrigerated (1-8°C) 1-2 weeks before analyses.

II: Samples stood at 20-25°C 3-6 weeks before analyses. Trihalomethanes (THM) formation proceeded to reaction endpoints (terminal values).

III: Samples with and without chlorine reducing agent (quenched, terminal values) to assess effect of residual chlorine and reaction time.

[c]Quenched samples preserved with sodium thiosulfate

[d]Samples shipped iced, stored 1-2 weeks refrigerated before analyses.

[e]Terminal samples not treated with thiosulfate.

[f]Minimum quantification limits.

04/15/85

The results with respect to the bromochloromethanes are listed in Table 3-3. Bromodichloromethane was detected in 57.8% of the water supplies tested while dibromochloromethane was detected in a 42.9% of the water supplies.

Minear (1978) monitored 21 drinking water supplies in the state of Tennessee and reported the presence of both bromodichloromethane and dibromochloromethane in all but one water supply. The concentrations of bromodichloromethane and dibromochloromethane ranged from 0.05-5.32 and 0.03-0.65 µg/ℓ, respectively. The mean concentrations of bromodichloromethane and dibromochloromethane in the treated water at the water supplies were 2.15 and 0.16 µg/ℓ, respectively. The author also reported slightly higher values for these two bromochloromethanes in water from distribution networks than from water obtained at the treatment plant. Similarly, Allgeier et al. (1980) monitored finished water at 15 water treatment plants in Kentucky and reported the presence of bromodichloromethane in all the water samples at a concentration range of <5-15 µg/ℓ, with a mean concentration of 9 µg/ℓ. Dibromochloromethane, however, was not detected in water from six supplies. The remaining nine supplies contained dibromochloromethane at concentrations <5 µg/ℓ.

Data available from the U.S. EPA STORET Data Base regarding the gross analyses of bromodichloro- and dibromochloromethane are listed in Table 3-4. The STORET DATA Base had no data for the other bromochloromethanes.

3.2. FOOD

In accordance with the Food and Drug Administration's Total Diet Market Basket Study, Entz et al. (1982) purchased 39 different food items at retail markets in three geographical areas (Elizabeth, NJ; Chapel Hill, NC; Washington, DC). Twenty food composites, comprising four different food groups

TABLE 3-3

Groundwater Supply Survey for Bromodichloromethane and Dibromochloromethane[a]

Bromochloromethanes	Positive Occurrences		Median of Positive (µg/ℓ)	Maximum Value (µg/ℓ)
	Number	Percent		
Bromodichloromethane				
Summary of:				
280 random sites[b]	100	35.1	1.4	60
186 random sites[c]	101	54.3	1.6	71
321 nonrandom sites[b]	144	44.9	2.0	49
158 nonrandom sites[c]	100	63.3	2.2	110
Dibromochloromethane				
Summary of:				
280 random sites[b]	87	31.1	2.1	52
186 random sites[c]	96	51.6	2.9	59
321 nonrandom sites[b]	135	42.1	3.5	63
158 nonrandom sites[c]	87	55.1	4.6	51

[a]Source: Westrick et al., 1984

[b]Sites serving <10,000 persons

[c]Sites serving >10,000 persons

TABLE 3-4

Gross Analyses for Bromodichloromethane and Dibromochloromethane*

Bromochloromethanes	Number of Samples	Concentration Range	Mean Concentration
Bromodichloromethane:			
Water	19,550	0-10133 µg/ℓ	11.14 µg/ℓ
Sediment	581	0-55 µg/kg	10.8 µg/kg
Tissue(fish)	430	0-25 µg/kg	0.625 µg/kg
Dibromochloromethane:			
Water	18,616	0-10133 µg/ℓ	10.09 µg/ℓ
Sediment	590	0-237 µg/kg	11.3 µg/kg

*Source: U.S. EPA STORET

(dairy, meats, oils-fats, beverages), were analyzed for bromodichloromethane. Bromodichloromethane was detected in one dairy composite at a concentration of 1.2 ppb and in two beverage composites at concentrations of 0.3 and 0.6 ppb. Subsequent analysis of cola soft drinks resulted in three positive detections at concentrations of 2.3, 3.4 and 3.8 ppb. Bromodichloromethane was detected at a level of 7 ppb in butter.

Pellizzari et al. (1982) collected mother's milk from selected women in four urban areas (Bridgeville, PA; Bayonne, NJ; Jersey City, NJ; and Baton Rouge, LA) in which emissions of halogenated pollutants seemed probable. Dibromochloromethane and dibromodichloromethane were each found once in a total of 12 samples analyzed by GC/MS.

Abdel-Rahman (1982) analyzed various soft drinks for the presence of bromodichloromethane. Cola beverages averaged 0.9-5.9 ng/mℓ bromodichloromethane while clear soft drinks had levels of 0.1-0.2 ng/mℓ. Municipal water supplies from which the soft drinks were manufactured were found to contain up to 20 ng/mℓ of trihalomethanes.

Bauer (1981) analyzed various milk products (e.g. ice cream, yogurt, curds and buttermilk) in Germany for the presence of organic halogenated compounds. In 12 samples that were analyzed, dibromochloromethane was found to have a mean concentration of 0.1 µg/kg with a range of not detectable to 0.3 µg/kg. Dibromochloromethane was also detected (at a level of 0.9 µg/kg) in one of seven cough syrups analyzed.

Ho et al. (1983) isolated and identified a total of 135 volatile organic compounds in fried bacon that was produced at a local supermarket and fried under normal conditions. Bromotrichloromethane was one of the compounds detected, but concentrations were not reported.

3.3. INHALATION

DeCarlo (1979) examined the air, water, and soil environment surrounding the bromine industry in El Dorado and Magnolia, Arkansas for brominated chemicals. Bromodichloromethane was present in air samples; however, concentrations were not given.

Brodzinsky and Singh (1982) compiled ambient air monitoring data for 151 chemicals from available sources that include various EPA monitoring studies. The data available for the bromochloromethanes are presented in Table 3-5; these data were primarily obtained from EPA documents and studies, including source monitoring data from chemical manufacturing and user facilities.

Bauer (1981) analyzed the ambient air of several German cities for the presence of halogenated organic compounds. The concentrations of dibromochloromethane ranged from not-detectable to 0.1 $\mu g/m^3$; however, one sample in the industrial city of Bochum-city was quantified at 0.9 $\mu g/m^3$.

Smith et al. (1983) suggested that bromodichloro- and dibromochloromethane are released in atmospheric emissions from electric power plant cooling systems. They detected these compounds in cooling recirculation water after chlorination treatment to the water. The evaporation from the cooling towers or ponds (coupled with the high volatility of the compounds) can be a potential source of these bromochloromethanes in the air.

3.4. DERMAL

Uptake of halomethanes from dermal exposure can occur under certain circumstances; however, there is no evidence in the available literature that dermal exposure contributes significantly to the total dose of bromochloromethanes for the general public (U.S. EPA, 1980b).

Bauer (1981) identified dibromochloromethane in various German cosmetic products at maximum levels of 0.2 $\mu g/\ell$.

TABLE 3-5

Ambient Air Monitoring for Bromochloromethanes[a]

Site	NPTS[b]	NZER[c]	Mean Concentration (ppt)
Bromodichloromethane			
Beaumont, TX	11	0	180
Chapel Hill, NC	6	0	120
El Dorado, AR	7	1	1.4
El Dorado, AR	40	40	C
Magnolia, AR	2	0	0.76
Magnolia, AR	15	15	0
Dibromochloromethane			
Beaumont, TX	11	0	14
Chapel Hill, NC	6	0	14
El Dorado, AR	40	35	0.48
Lake Charles, LA	4	0	19
Magnolia, AR	28	28	0
Dibromodichloromethane			
El Dorado, AR	2	0	24

[a]Source: Brodzinsky and Singh, 1982

[b]NPTS is the number of data points for location.

[c]NZER is the number of data points below the minimum detection limit.

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism or excretion of tribromochloromethane or dibromodichloromethane were not located in the available literature cited in the Appendix.

4.1. ABSORPTION

Although pertinent data regarding the absorption of bromochloromethane, bromodichloromethane, bromotrichloromethane or dibromochloromethane were not located in the available literature, toxicity studies (Chapter 5) indicate that these halomethanes are absorbed after ingestion. Anderson et al. (1980) measured the uptake of bromochloromethane from an inhalation chamber by rats. Based on the uptake curves, the maximum rate of uptake of bromochloromethane was 11.4 mg/kg/hour in male Fischer 344 rats exposed to 119 ppm of bromochloromethane.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of bromochloromethane and dibromochloromethane were not located in the available literature cited in the Appendix.

A group of 12 male Sprague-Dawley rats were treated daily by gavage with 0, 0.5 or 5 mg/day of bromodichloromethane for 25 days (Pfaffenberger et al., 1979). One rat from each group was killed every 3 or 4 days during the dosing schedule and 3 and 6 days after the dosing had been completed. During treatment with 0.5 or 5 mg/day of bromodichloromethane, the serum contained 1 ppm and 23 ppm, respectively, of bromodichloromethane, and the adipose tissue contained 51 and 1800 ng/g, respectively, of bromodichloromethane. Within 3-6 days after dosing had been completed, the serum contained 1 ppm of bromodichloromethane and the adipose tissue contained 3-4

ng/g of bromodichloromethane, regardless of the dose administered. Pfaffenberger et al. (1979) concluded that the amount of bromodichloromethane stored in the fat did not increase with time and that practically all of the bromodichloromethane had been eliminated from serum and fat within 3-6 days after treatment.

After 0.1-0.5 mℓ of bromotrichloromethane was administered by gavage to Wistar rats, bromotrichloromethane was detectable in the liver within 15 minutes, reached its peak liver concentration of ~1.1 mg/g of liver within 30 minutes, returned to its level detected 15 minutes after treatment within 120 minutes and remained at that level for the duration of the experiment (240 minutes) (Bini et al., 1975).

4.3. METABOLISM

Metabolism of inhaled bromochloromethane followed the kinetics of both a first-order and a saturable reaction (Andersen et al., 1980; Andersen, 1981; Gargas and Andersen, 1982).

Intraperitoneal injection of (3.0 mmoles/kg) radioactive ^{14}C-bromochloromethane resulted in the elevation of circulating carboxyhemoglobin in male Long-Evans rats weighing 200-350 g (Kubic et al., 1974). A maximum saturation of ~5% carboxyhemoglobin occurred 4 hours after treatment with bromochloromethane and was interpreted as an indication of carbon monoxide production during the metabolism of bromochloromethane (Kubic et al., 1974). In a subsequent study, Anders et al. (1978) reported that blood carbon monoxide levels were higher after rats were intraperitoneally injected with dibromochloromethane than after they were intraperitoneally injected with bromodichloromethane. In neither case did carbon monoxide levels approach that produced when bromoform or iodoform were injected intraperitoneally (Anders et al., 1978).

Wistar rats weighing ~200 g and fasted for 24 hours were treated by gavage with 0.1-0.5 mL of bromotrichloromethane (Bini et al., 1975). Groups of 5 rats were killed 15, 30, 120 and 240 minutes after treatment and their livers subsequently analyzed. Bromotrichloromethane was detectable in the liver 15 minutes after treatment, rose to its highest concentration (~1.1 mg/g of liver) by 30 minutes after treatment, and was back to a level equivalent to that detected 15 minutes after treatment at both 120 and 240 minutes after treatment. At 15 minutes after treatment, chloroform ($CHCl_3$) and carbon tetrachloride (CCl_4) were the only metabolites of bromotrichloromethane identified in the liver; however by 30 and 240 minutes after treatment bromodichloromethane ($CHBrCl_2$) and the compound (C_2Cl_6) were identified as metabolites of bromotrichloromethane in addition to chloroform and carbon tetrachloride (Bini et al., 1975).

Pohl et al. (1981) reported that bromotrichloromethane was metabolized to phosgene ($COCl_2$), or possibly COBrCl, by rats in vivo and by rat liver microsomes in vitro. They further postulated that phosgene reacted with glutathione and may account for the glutathione-depleting property of bromotrichloromethane. Waller and Recknayel (1982) also reported that phosgene may be a metabolite of bromotrichloromethane.

4.4. EXCRETION

Pertinent data regarding the excretion of bromochloromethane, bromodichloromethane, bromotrichloromethane or dibromomethane were not located in the available literature cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

Groups of 20 strain A/St male mice (6-8 weeks old) were given intraperitoneal injections of 20, 40 or 100 mg/kg of bromodichloromethane (in tricaprylin) 3 times a week for a total of 18 injections for the low-dose group and 24 injections for the middle- and high-dose group (Theiss et al., 1977). The high dose was predetermined to be the MTD. The surviving mice (15 in the low dose, 16 in the middle dose and 13 in the high dose) were sacrificed 24 weeks after the first injection. After fixation, the lungs were examined with a dissecting scope and areas of surface adenomas identified. Some of the nodules were subsequently evaluated histologically. The number of lung tumors per mouse was not significantly increased at any dose level of bromodichloromethane; however, the increase in the number of pulmonary adenomas in the mice treated with 100 mg/kg of bromodichloromethane was approaching statistical significance ($p=0.067$). The number of lung tumors per mouse was 0.19, 0.20, 0.25 and 0.85 in the controls, low-, middle- and high-dose groups, respectively.

Aldrich and Peoples (1982) examined the possible association of a high level of malignant melanoma in Brevard County, Florida with levels of trihalomethanes in the drinking water. The county was divided into three regions having low, median and high levels of trihalomethanes. Chloroform and bromodichloromethane were the major water contaminants with lesser amounts of dibromochloromethane and still lesser amounts of bromoform. The survey of melanoma cases showed a relationship between observed new cases of melanoma (between 1975 and 1977) and levels of trihalomethanes in the water. Although there was some association between the levels of the bromochloromethanes and melanoma (Table 5-1), chloroform was related in a dose-related

TABLE 5-1

Bromochloromethanes[a]

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value)
Water; drinking and dermal	92,754	National Survey Data	MS	0-60 ppb[b] 0-80 ppb[c]	lifetime	skin	melanoma	4	10.73	0.373
Water; drinking and dermal	108,561	National Survey Data	MS	2-6 ppb[b] 1-4 ppb[c]	lifetime	skin	melanoma	13	12.56	1.035
Water; drinking and dermal	63,011	National Survey Data	MS	75-250[b] 50-100[c]	lifetime	skin	melanoma	19	7.29	2.606

QUALITY OF EVIDENCE

Strengths of Study: Large groups of people were grouped according to the levels of trihalomethanes in their water source. Comparisons of melanoma incidence and National Cancer Survey Data were made according to trihalomethane exposure.

Weaknesses of Study: The population studied lived in Florida where sunlight exposure is high. Exposures were to many chemicals as is often the case in human studies. Base levels of the bromochloromethanes were not determined or estimated.

Overall adequacy: Limited

Comments: The incidence of melanoma showed a dose-related response when compared with the level of chloroform in the water source. Chloroform and bromoform were also found in water samples.

[a]Source: Aldrich and Peoples, 1982

[b]Bromodichloromethane

[c]Dibromochloromethane

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manner. Levels of chloroform in the water were also higher than either bromochloromethane compound. Two other factors cannot be ignored, age and sunlight. The entire population of Brevard County is older (retirees) and inclined to outdoor activities. However, taking these factors into account, the above data suggests a relationship between increased cancer risk and trihalomethanes.

Using cancer incidence data for the state of Iowa, Isacson et al. (1983) attempted to correlate the source of drinking water and its trihalomethane contaminants with specific types of cancer. Levels of chloroform, bromodichloromethane and dibromochloromethane ranged from 0-900, 0-220 and 0-17.0 µg/ℓ, respectively. When cancer cases were categorized as to the levels of each contaminant in their drinking water, a slight dose-related increase in the incidence of bladder cancer in males, lung cancer in males, and rectal cancer in both sexes was noted for bromodichloromethane. The incidence of bladder cancer in males, breast cancer in females, and stomach cancer in males was elevated in a dose-related manner when categorized by dibromochloromethane exposure. The significance of these increased cancer incidences relative to exposure levels of the bromochloroethanes was not discussed. In most cases, the incidence of cancers of a specific type were only slightly elevated in the high exposure group compared with the low exposure group. The authors (Isacson et al., 1983) proposed that these data do suggest an association between the level of trihalomethanes (including chloroform) in drinking water and bladder cancer in males, lung cancer in females and rectal cancer in both species.

A carcinogenesis bioassay in rats and mice given bromodichloromethane by gavage is currently being conducted by the NTP (Powers, 1980); evaluation of the chronic histopathology is in progress (NTP, 1984).

Pertinent data regarding the carcinogenicity of bromochloromethane, bromotrichloromethane, tribromochloromethane or dibromodichloromethane were not located in the available literature cited in the Appendix.

5.2. MUTAGENICITY

The mutagenicity studies of bromochloromethanes are summarized in Table 5-2. Various publications of the same data (Simmon, 1978; Simmon et al., 1977; Simmon and Tardiff, 1978) indicate that bromochloromethane, bromodichloromethane and dibromochloromethane gave a positive dose-related response for reverse mutation without metabolic activation in Salmonella typhimurium strain TA100 The dose-response curves indicated that the response was greatest with bromochloromethane, followed by dibromochloromethane and then bromodichloromethane.

Osterman-Golkar et al. (1983) also obtained positive responses for bromochloromethane in reverse mutation assays in strain TA100 and TA1535 of S. typhimurium and strain Wu361089 of Escherichia coli, and for forward mutation in E. coli strains Sd-4 and K39. Metabolic activation was not necessary.

Borzelleca and Carchman (1982) found that dibromochloromethane was negative in a dominant lethal study conducted in ICR mice. Males of the F_0 and F_{1b} generations of a multigeneration study (Section 5.4.) in which dibromochloromethane was administered in the drinking water at 0, 0.1, 1.0 or 4.0 mg/mℓ were mated with untreated females for 7 days, and the females were sacrificed 14 days from the mid-point of the mating period.

Bromodichloromethane and dibromochloromethane treatment resulted in dose-related increased incidences of sister chromatid exchange in mouse bone marrow cells following oral treatment of male mice with 0, 25, 50 or 100 mg/kg/day for 4 days and in human lymphocytes treated in vitro (Morimoto and Koizumi, 1983).

TABLE 5-2

Mutagenicity Testing of Bromochloromethanes

Assay	Indicator/ Organism	Compound	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA100	bromochloro-methane	liquid incubation	0, 20, 40, 60 mM	none	+	Dose-related increase in the number of revertants/plate up to 40 mM.	Osterman-Golkar et al., 1983
Reverse mutation	S. typhimurium TA100 TA1535	bromochloro-methane	vapor phase	10 µL/plate	none	+ +	The compound was placed on the inside of the Petri dish lid, and the covered plates were placed within a dessicator. The response was 3-fold greater in TA100 than TA1535.	Osterman-Golkar et al., 1983
Reverse mutation	S. typhimurium TA100	bromochloro-methane	vapor phase	0, 10, 20, 50 µL/dessicator	none	+	Dose-related increase in number of revertants/plate up to 50 µL with a maximum of ~4500 revertants/plate.	Simmon, 1978; Simmon et al., 1977; Simmon and Tardiff, 1978
Reverse mutation	S. typhimurium TA100	bromodi-chloromethane	vapor phase	0, 25, 50, 75, 100, 250 µL/ dessicator	none	+	Dose-related increase in number of revertants/plate up to 100 µL with a maximum of ~475 revertants/plate.	Simmon, 1978; Simmon et al., 1977; Simmon and Tardiff, 1978
Reverse mutation	S. typhimurium	dibromo-chloromethane	vapor phase	0, 5, 10, 15, 25, 50 µL/dessicator	none	+	Dose-related increase in number of revertants/plate up to 15 µL with a maximum of ~650 revertants/plate.	Simmon, 1978; Simmon et al., 1977; Simmon and Tardiff, 1978
Reverse mutation	Escherichia coli Wu361089	bromochloro-methane	vapor phase	10 µL/plate	none	+	The compound was placed on the inside of the Petri dish lid, and the covered plates were placed in a dessicator.	Osterman-Golkar et al., 1983
Forward mutation	E. coli Sd-4	bromochloro-methane	vapor phase	10 µL/plate	none	+	The compound was placed on the inside of the Petri dish lid, and the covered plates were placed in a dessicator. The response was weakly positive.	Osterman-Golkar et al., 1983

TABLE 5-2 (cont.)

Assay	Indicator/ Organism	Compound	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Forward mutation (prophage induction)	E. coli K394	bromochloro-methane	vapor phase	10 µl/plate	none	+	The compound was placed on the inside of the Petri dish lid, and the covered plates were placed in a dessicator.	Osterman-Golkar et al., 1983
Dominant lethal	offspring of treated male and untreated female ICR mice	dibromo-chloromethane	F_0 and F_{1b} males from a reproduction study exposed	0, 0.1, 1.0 or 4.0 mg/ml in drinking water	NA	-	No effects on number of early resorptions, late resorptions or total resorptions, number of litters, implantations/dam, live fetuses/litter.	Borzelleca and Carchman, 1982
Sister chromatid exchange	mouse bone marrow	bromodi-chloromethane	dosing of adult male ICS/SJ mice by gavage	0, 25, 50, 100 or 200 mg/kg/day	NA	+	Dose-related increase up to 100 mg/kg/day; at 200 mg/kg/day, all mice died.	Morimoto and Koizumi, 1983
Sister chromatid exchange	mouse bone marrow	dibromo-chloromethane	dosing of adult male ICS/SJ mice by gavage	0, 25, 50, 100 or 200 mg/kg/day	NA	+	Dose-related increase up to 100 mg/kg/day; at 200 mg/kg/day, all mice died; the magnitude of the response was similar to that with bromodichloromethane.	Morimoto and Koizumi, 1983
Sister chromatid exchange	human lymphocytes	bromodi-chloromethane	in vitro culture	1.6×10^{-9} to 5×10^{-2} M	none	+	The lowest concentration to cause a significant ($p<0.05$) increase above control was 4×10^{-4} M.	Morimoto and Koizumi, 1983
Sister chromatid exchange	human lymphocytes	dibromo-chloromethane	in vitro culture	1.6×10^{-9} to 5×10^{-2} M	none	+	The lowest concentration to cause a significant ($p<0.05$) increase above control was 4×10^{-4} M.	Morimoto and Koizumi, 1983

NA = Not applicable

Analysis of the mutagenicity of drinking water is obfuscated by the plethora of contaminants found in drinking water and by the great variability of the relative concentration of those contaminants; relative concentrations vary from place to place and from the time of one sampling to the time of the next. Nestmann et al. (1983) reported a positive correlation between the mutagenicity in S. typhimurium strains TA98 and TA100 of Canadian drinking water from various sources and the presence of bromodichloromethane and dibromochloromethane, among many other volatile organic compounds such as benzene, toluene and chloroform. Williams et al. (1982), however, in an earlier publication by some of the same investigators, reported that "no relationship between mutagenic activity [of Canadian drinking water] and the presence of individual or groups of chemicals could be deduced."

Pertinent data regarding the mutagenicity of bromotrichloromethane, tribromochloromethane or dibromodichloromethane were not located in the available literature cited in the Appendix.

5.3. TERATOGENICITY

Groups of 9-14 pregnant Spague-Dawley rats were treated by gavage with 0, 50, 100 or 200 mg/kg/day of dibromochloromethane, or with 0, 50, 100 or 200 mg/kg/day of bromodichloromethane, on days 6-15 of gestation (Ruddick et al., 1983). The day on which sperm-positive vaginal smears were obtained was defined as day 1 of gestation. All compounds were dissolved in corn oil and administered at 1 mℓ/100 g bw. Control females were treated only with corn oil. Body weights were recorded on day 1 and days 6-15 of gestation as well as before and after Caesarean section on day 22. The fetuses were removed by Caesarean section on day 22 and examined for external malformations; two fetuses from each litter were evaluated histologically, while others were prepared for evaluation of skeletal and visceral development.

Hematological (hematocrit, hemoglobin concentration, erythrocyte and leukocyte counts, mean corpuscular hemoglobin concentration and mean corpuscular volume) and biochemical (serum sodium, potassium, inorganic phosphorus, calcium, total bilirubin, total protein, GOT, cholesterol, glucose, uric acid, alkaline phosphatase, lactic dehydrogenase and sorbitol dehydrogenase) evaluations were performed on the dams. In addition, maternal liver, heart, brain, spleen and one kidney were weighed and examined for gross pathological alterations. Histological evaluations of the major organs from five dams in the highest dose groups and in the control group were made. Additional histological evaluations were performed only if warranted. Hepatic mixed function oxidase enzyme (aniline hydroxylase and aminopyrine demethylase) activities were determined to evaluate their induction. Bromodichloromethane at the highest dose (200 mg/kg/day) significantly ($p<0.05$) decreased maternal weight (25% reduction) and increased relative kidney weight and brain weight. At all dose levels tested (50, 100 and 200 mg/kg/day), bromodichloromethane significantly ($p<0.05$) increased the relative liver weight in the dams; however, no hematological or biochemical parameters were affected. The only maternal effect of dibromochloromethane was a decrease in maternal body weight (38% reduction) at the highest dose tested (200 mg/kg/day). There were no adverse effects of either bromodichloromethane or dibromochloromethane on the gross appearance or health of the fetuses. Treatment with dibromochloromethane was not associated with any increased incidence of skeletal or visceral abnormalities. The high dose (200 mg/kg/day) of bromodichloromethane, however, did alter the histological pattern of ossification in the parietal bone. There were also dose-related increased incidences of aberrations in the sternebrae. The number of fetuses affected/the number of litters affected were 2/2, 8/4, 9/7 and 10/6 at 0, 50, 100 and 200 mg/kg/day, respectively.

Teratological screening of dibromochloromethane was reported by Borzelleca and Carchman (1982) in the F_{1c} and F_{2b} generation of a multi-generation reproductive study described in more detail in Section 5.4. Treated females of the F_0 and F_{1b} generation were mated to untreated males and were sacrificed on day 18 of gestation. The results of the teratological part of the Borzelleca and Carchman (1982) study are summarized in Table 5-3 and 5-4. As indicated in Table 5-3, there was no significant effect on the number of gross, visceral or skeletal variations in the offspring of F_0 or F_{1b} mice exposed to 0.1, 1.0 or 4.0 mg of dibromochloromethane/mℓ of drinking water. Data concerning numbers of litters, implantations/dam, live fetuses/litter and resorptions are presented in Table 5-4. None of these endpoints were statistically different from the control incidences as reported by Borzelleca and Carchman (1982).

Groups of pregnant CD-1 mice were treated by gavage on days 7-14 of gestation with a synthetic mixture of volatile compounds believed to be present in the drinking water of 110 cities at dose levels estimated to be 300, 1000 and 3000 times the human exposure level (~3 µg/kg/day) (Kavlock et al., 1979). The volatile mixture, administered in DMSO, contained by weight 68.9% chloroform, 16.4% bromodichloromethane, 10.0% dibromochloromethane, 3.6% bromoform and <1% 1,2-dichloroethane, 1,1,1-trichloroethane, carbon tetrachloride, trichloroethylene, tetrachloroethylene, benzene, o-dichlorobenzene, m-dichlorobenzene and p-dichlorobenzene. The dams were killed on day 18 of gestation and the only reported effect was a dose-related increase in maternal weight gain. The mixture of volatile compounds had no effect on maternal liver weight, fetal weight, the number of implantations/litter or on the size, mortality, skeletal or visceral development of the fetus.

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TABLE 5-3

Incidence of Fetal Developmental Variations in the Offspring of Mice Exposed to Dibromochloromethane in the Drinking Water[a]

	F_{1c} Generation					F_{2b} Generation				
Concentration (mg/mL)	0.0[b]	0.0[c]	0.1	1.0	4.0	0.0.[b]	0.0[c]	0.1	1.0	4.0
Number of fetuses examined (number of litters)	75 (6)	67 (6)	70 (6)	49 (6)	44 (6)	24 (3)	65 (6)	59 (6)	25 (6)	32 (6)
Number of gross malformations (number of litters)	1 (1)	0	0	1 (1)	1 (1)	0	0	0	0	1
Number of visceral variations (number of litters)	1 (1)	0	0	1 (1)	1 (1)	0	0	1 (1)	0	0
Number of skeletal variations (number of litters)	0	4 (1)	0	4 (2)	0	NR	NR	NR	NR	NR

[a]Source: Borzelleca and Carchman, 1982

[b]Untreated control

[c]Vehicle control

NR = Not reported

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TABLE 5-4

Results of Teratology Screening in the Offspring of Mice Exposed to Dibromochloromethane in the Drinking Water[a]

	F_{1c} Generation					F_{2b} Generation				
Concentration (mg/mℓ)	0.0[b]	0.0[c]	0.1	1.0	4.0	0.0[b]	0.0[c]	0.1	1.0	4.0
Number of litters	6	6	6	6	6	3	6	6	6	6
Implantations/Dam[d]	13±2	16±5	13±6	11±6	8±6	10±6	11±6	12±2	12±2	7±6
Live fetuses/litter[d]	13±2	11±3	12±3	10±3	7±3	8±4	11±3	10±3	4±3	5±3
% of implants resorbed	7	31	7	9	13	20	3	16	66	29
Sex ratio M:f	46:54	38:62	50:50	50:50	40:60	50:50	47:53	52:48	50:50	50:50

[a]Source: Borzelleca and Carchman, 1982

[b]Untreated control

[c]Vehicle control

[d]Mean ± SD

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Pertinent data regarding the teratogenicity of bromochloromethane, bromotrichloromethane, tribromochloromethane or dibromodichloromethane were not located in the available literature cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Groups of 10 male and 30 female IRC mice were treated with dibromochloromethane in emulphor (a polyoxyethylated nonionic surfactant oil) at concentrations of 0, 0.1, 1.0 or 4.0 mg/mℓ of in the drinking water (Borzelleca and Carchman, 1982). The mice were 9 weeks old at the beginning of treatment, which was continuous throughout the experiment. After 35 days of treatment the animals were mated to produce the F_{1a} generation. Subsequent matings of the F_0 mice produced F_{1b} and F_{1c} generations. The F_{1b} generation received the same dose level of dibromochloromethane as their parents in the drinking water for 11 weeks beginning after weaning at 3 weeks of age. When the F_{1b} generation was 14 weeks old, mating to produce the F_{2a} generation was conducted. The animals were subsequently remated to produce the F_{2b} generation. Teratological evaluation (see Section 5.3.) and the dominant lethal study (see Section 5.2.) were done with the F_{1c} and F_{2b} generations.

Dibromochloromethane, at a concentration of 4 mg/mℓ of drinking water, significantly decreased the average terminal body weight of both males and females and caused gross liver pathology in 100% of the treated mice; 18% of the F_0 mice and 15% of the F_{1b} adults displayed severe liver pathology, defined as large nodules ($\geq$3 mm) on the liver surface. The investigators stated that the liver morphology was characteristic of hepatotoxicity; however, histologic examination was not performed. Survival of the F_1 generation was decreased in mice treated with 4 mg/mℓ of dibromochloromethane in the drinking water. In addition, litter size, gestation index

and the viability of the pups were also significantly reduced. Lactation index and postnatal body weight were reduced only in the F_{2b} generation after exposure to 4 mg/mℓ of dibromochloromethane. No significant increase in malformations was reported at any dose level (see Section 5.3.). The results of the dominant lethal assay were also negative at all dose levels tested (see Section 5.2.).

At a concentration of 1 mg/mℓ of dibromochloromethane in the drinking water, there was a significant decrease in the average terminal body weight of females. Gross liver pathology was present in 70% of the F_0 mice and 64% of the F_{1b} mice; the lesions varied in severity from fat accumulation to distinct masses on the liver surface. Although not present in every generation, there were significant decreases in litter size, pup viability, postnatal body weight and the lactation index in the mice treated with 1 mg/mℓ of dibromochloromethane.

Exposure to 0.1 mg/mℓ of dibromochloromethane in the drinking water resulted in a significant decrease in the postnatal body weight of pups in the F_{2b} generation, which remained significantly reduced at 21 days after birth. Adult mice of the F_0 and F_{1b} generation had gross liver lesions characterized by yellow color presumed to be due to accumulation of fat. No other significant effects at 0.1 mg/mℓ were reported (Borzelleca and Carchman, 1982).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

5.5.1. Bromodichloromethane and Dibromochloromethane. No studies utilizing chronic exposure durations were located in the available literature. However, a number of studies of shorter duration have been described. Groups of 20 male and 20 female weanling Sprague-Dawley rats were treated with 0, 5, 50, 500 or 2500 ppm of bromodichloromethane or 0, 5, 50, 500 or

2500 ppm of dibromochloromethane dissolved in 1% Emulphor in the drinking water for 90 days (Chu et al., 1982b). The actual dose levels of bromodichloromethane were calculated from experimental data by Chu et al. (1982b) and reported to be 0, 0.14, 1.6, 13.0 or 49.0 mg/rat/day for the males and 0, 0.13, 1.2, 9.8 or 32.0 mg/rat/day for the females. The actual dose levels of dibromochloromethane were calculated from experimental data by Chu et al. (1982b) and reported to be 0, 0.14, 1.5, 12.0 or 55.0 mg/rat/day for the male and 0, 0.11, 1.2, 9.5 or 38.0 mg/rat/day for the females. At the end of the 90-day treatment period 10 rats/sex/group were killed; the remaining rats were maintained without further treatment for an additional 90 days. Records of animal body weight and food consumption were kept throughout the experiment. Upon sacrifice, levels of serum sodium, calcium, potassium, inorganic phosphorus, total bilirubin and protein, cholesterol, glucose, uric acid, akaline phosphatase, lactate dehydrogenase and sorbitol dehydrogenase were determined. Hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, the number of platelets and the cellularity of the bone marrow were evaluated as well as performing an erythrocyte, and a total and differential leukocyte count. The brain, liver, spleen, kidney and heart were weighed. Parts of the brain pituitary, liver, adrenal, thyroid, parathyroid, thymus, lungs, trachea, bronchi, thoracic aorta, esophagus, gastric cardia, fundus and pylorus, duodenum, pancreas, colon, kidney, spleen, bone marrow, mesenteric and mediastinal lymph nodes, testes, epididymis, skeletal muscle and heart were fixed in formalin and prepared for histological evaluation. Pieces of liver were evaluated for fatty necrosis in frozen sections. Although food consumption was decreased in rats treated with both bromodichloromethane and dibromochloromethane, only the rats (both male and

female) treated with 2500 ppm (49.0 mg/rat/day for males; 32.0 mg/rat/day for females) of bromodichloromethane had significantly decreased body weight after the 90 days of treatment. Subsequent to the 90-day recovery period, however, there was no significant difference between the body weight of the treatment rats and the control rats although the treated rats appeared to consume significantly less food.

Treatment with bromodichloromethane or dibromochloromethane did not result in any statistically significant effect on the biochemical parameters studied. Although lactate dehydrogenase levels were reduced, the reduction was not statistically significant (1224±654 high-dose group and 1558±309 mLu/mL controls).

There was a statistically significant reduction in the number of lymphocytes in female rats given 2500 ppm (32.0 mg/rat/day) of bromodichloromethane at the end of the recovery period, but apparently not at the end of the treatment period.

Histological examination revealed alterations in the microanatomy of the liver and thyroid at the end of the 90-day treatment period, but not at the end of the 90-day recovery period. Histopathological changes in the liver included fatty infiltration of hepatocytes and hyperplasia of the biliary epithelium. Liver lesions occurred in male and female rats at all levels of exposure to both bromodichloromethane and dibromochloromethane; however, a higher incidence of liver lesions in vehicle (Emulphor) treated rats as compared with tap water treated rats obfuscates the interpretation of the experimental results. Although the incidence of hepatic lesions did not appear to increase in a dose-related manner, the severity of the liver lesions appeared to increase as the dose level of bromodichloromethane and dibromochloromethane increased. When the liver lesions were graded for

severity on a scale of 1-10, the mean severity differed significantly from controls ($p<0.05$) at $\geq$50 ppm in males and at 50 and 2500 ppm in females receiving bromodichloromethane and at 2500 ppm in males and at 50 and 2500 ppm in females receiving dibromochloromethanes. The severity of liver lesions of treated rats were not significantly different from the control rats after the 90-day recovery period.

Thyroid gland changes (decreased follicle size and increased epithelial height) after 90 days of treatment with bromodichloromethane and dibromochloromethane were not significantly different from controls.

In a shorter-term study, Chu et al. (1982b) found no effects on growth rate, food intake, hematologic and biochemical parameters or histology in groups of 10 male Sprague-Dawley rats given bromodichloromethane or dibromochloromethane in the drinking water at 0, 5, 50 or 500 ppm for 28 days. The drinking water concentrations corresponded to daily doses of 0, 0.14, 1.4 or 12 mg/rat/day for bromodichloromethane and 0, 0.13, 1.4 or 12 mg/rat/day for dibromochloromethane. Rats receiving 12 mg/rat/day of bromodichloromethane had slightly increased relative kidney weights.

Exposure to bromodichloromethane and dibromochloromethane in the drinking water for 10 days at a dose of 200 mg/kg/day caused fat degeneration, an altered endoplasmic reticulum and a decrease in the mitochondrial diameter in the livers of rats. Exposure at lower dose levels was reported to have no effect (Nishimura et al., 1980).

Groups of 7-11 adult male ICR mice were treated by gavage with 1.2 or 11.6 mg/kg/day of bromodichloromethane, or 1.0 or 10.0 mg/kg/day of dibromochloromethane, suspended in emulphor: water (1:8), for a period of 90 days (Balster and Borzelleca, 1982). These dose levels represent 300 and 3000 times, respectively, the concentration of water samples. Control groups of 6-8 male mice received no treatment or were treated with the vehicle alone.

Behavioral testing, which consisted of the screen, the hole-board and the cling test and which were conducted within 3 days after completion of the 90-day treatment, indicated that bromodichloromethane and dibromochloromethane did not significantly affect the behavioral parameters studied. In another experiment also reported by Balster and Borzelleca (1982), operant behavior was significantly affected after mice had been treated with 100 or 400 mg/kg/day of bromodichloromethane, or 400 mg/kg/day of dibromochloromethane for 60 days. Treatment of the mice at 100 mg/kg/day for 30 days had no effect on passive avoidance learning or initial step-through latency, and treatment of the mice at the two low doses of the compounds for 14 days had no effect on swimming endurance. Animal mortality was high when mice were treated with 100 or 400 mg/kg/day of bromodichloromethane or dibromochloromethane.

In two 90-day studies reported in abstract form, unspecified numbers of male and female ICR mice were treated with bromodichloromethane or dibromochloromethane beginning on day 7 after birth (Schuller et al., 1978; Munson et al., 1978). In the first study, mice were treated by gavage at dosages of the chemicals of 0, 0.2, 12.5 or 125 mg/kg/day to study the effects on humoral and cell-mediated immunity (Schuller et al., 1978). Dibromochloromethane had no effect on delayed hypersensitivity, while bromodichloromethane at 125 mg/kg/day resulted in 69% inhibition in female mice compared with controls. It was stated that delayed hypersensitivity was similarly depressed in males at 125 mg/kg/day bromodichloromethane. Bromodichloromethane at an unspecified dosage was reported to suppress humoral immunity by 43% in females compared with controls. Treatment with bromodichloromethane and dibromochloromethane had no effect on liver function, kidney function or hematologic parameters at any dose tested.

In the second study, the mice were treated by gavage with the chemicals at 0, 0.3, 12.5 or 125 mg/kg/day to study effects on the reticuloendothelial system function (Munson et al., 1978). For bromodichloromethane, there was no effect on phagocytic index, but there was a dose-related suppression of hepatic phagocytosis in males. The maximum suppression was 45% and occurred at 125 mg/kg/day. Hepatic phagocytosis was also suppressed 18% in females at 125 mg/kg/day bromodichloromethane. A dose-related decrease in hepatic phagocytosis was also observed in males and females treated with dibromochloromethane. Suppression of splenic phagocytosis by 27% at 12.5 mg/kg/day and 40% at 125 mg/kg/day was observed in males treated with dibromochloromethane.

Groups of 8-12 male and 8-12 female CD-1 mice were treated by gavage with 0, 50, 125 or 250 mg/kg/day of bromodichloromethane or 0, 50, 125, or 250 mg/kg/day of dibromochloromethane for 14 days (Munson et al., 1982). No vehicle-free control group was included, since the control and the treated animals both received an equivalent amount of Emulphor. Munson et al. (1982) anesthetized the mice with chloroform before removing blood and tissue samples at the end of the 14-day experiment. After 14 days exposure to 250 mg/kg/day of bromodichloromethane or dibromochloromethane, body weight and relative splenic weight were decreased, relative liver weight was increased, levels of SGOT and SGPT were increased and splenic lymphocyte counts (AFC cells that are indicative of humoral immunity) were decreased. At a dose of 125 mg/kg/day of bromodichloromethane, liver weight was increased and the amount of circulating fibrinogen was decreased. At a dose of 125 mg/kg/day of dibromochloromethane there was a significant decrease in AFC spleen cells. No effects were reported at the lowest dose tested (Table 5-5).

TABLE 5-5

Effects of Bromodichloromethane and Dibromochloromethane on CD-1 Mice Exposed for 14 Days by Gavage[a]

	Sex	Dose (mg/kg bw)	Bromodichloromethane	Dibromochloromethane
Body weight (g)	M	0	32.9 ± 0.6	32.3 ± 0.7
		50	33.2 ± 0.6	33.5 ± 1.0
		125	31.1 ± 1.0	31.7 ± 0.07
		250	25.8 ± 1.2[b]	25.8 ± 0.8[b]
	F	0	26.6 ± 0.4	29.9 ± 0.5
		50	26.0 ± 0.6	27.1 ± 0.7
		125	24.9 ± 0.6	26.1 ± 0.9
		250	21.5 ± 1.0[b]	26.3 ± 0.7[b]
Liver weights (mg)	M	0	1904 ± 65	1851 ± 72
		50	2050 ± 72	2148 ± 101
		125	2083 ± 115[b]	2376 ± 182[b]
		250	2851 ± 79[b]	2007 ± 105
	F	0	1432 ± 46	1528 ± 56
		50	1584 ± 73	1622 ± 61
		125	1608 ± 59[b]	1735 ± 93
		250	1553 ± 58[b]	1923 ± 62
Spleen weights (mg)	M	0	160 ± 12	162 ± 7
		50	143 ± 6	154 ± 10
		125	136 ± 10	145 ± 8
		250	99 ± 11[b]	91 ± 8[b]
	F	0	162 ± 7	NR
		50	136 ± 11	NR
		125	112 ± 7	NR
		250	82 ± 10[b]	NR

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TABLE 5-5 (cont.)

	Sex	Dose (mg/kg bw)	Bromodichloromethane	Dibromochloromethane
SGOT (IU/ℓ)	M	0	70 ± 10	97.9 ± 10.8
		50	159 ± 28	101.9 ± 10.3
		125	172 ± 19	102.8 ± 11.1
		250	643 ± 125[b]	474.6 ± 67.5[b]
	F	0	94 ± 10	112 ± 8
		50	85 ± 7	124 ± 17
		125	215 ± 38[b]	156 ± 17
		250	774 ± 51[b]	526 ± 53[b]
SGPT (IU/ℓ)	M	0	35 ± 2	48.6 ± 5.8
		50	91 ± 17	68.4 ± 7.9
		125	118 ± 29[b]	83.5 ± 11.1
		250	703 ± 12[b]	486 ± 61.9[b]
	F	0	50 ± 7	54 ± 6
		50	49 ± 3	73 ± 14
		125	184 ± 40[b]	107 ± 16
		250	648 ± 73[b]	449 ± 44[b]
Plasma fibrinogen (mg %)	M	0	320 ± 14	309 ± 10
		50	345 ± 15	310 ± 5
		125	283 ± 10	296 ± 8
		250	276 ± 17[b]	251 ± 15[b]
	F	0	226 ± 8	260 ± 6
		50	209 ± 7	259 ± 6
		125	191 ± 12	248 ± 10
		250	119 ± 21[b]	233 ± 7

[a]Source: Munson et al., 1982

[b]Significant at $p<0.05$ level, Dunnetts

NR = Not reported

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Groups of ~10 male CD-1 mice were treated by gavage with 37, 74 or 148 mg/kg/day of bromodichloromethane or 37, 74 or 147 mg/kg/day of dibromochloromethane for 14 consecutive days (Condie et al., 1983). A group of 16 male CD-1 mice were gavaged with corn oil only and served as the control group. Neither bromodichloromethane nor dibromochloromethane had a significant effect on the body weight of the mice or on the levels of blood urea nitrogen or creatine at any dose level tested. At the highest dose tested for both bromodichloromethane and dibromochloromethane and at the middle dose tested for bromodichloromethane, there was a significant decrease in the amount of p-aminohippurate taken up by a renal cortical slice in vitro, an indication of impaired proximal tubule function, as well as a significant increase at the highest dose tested in the level of SGPT (20.7 control and 50 IU/ℓ high-dose), an indication of impaired hepatic function. Histological evaluation of the kidneys indicated that there was intratubal mineralization, slight to moderate epithelial hyperplasia and minimal cytomegaly after treatment with 148 mg/kg/day of bromodichloromethane, and epithelial hyperplasia and a dose-related increase in mesangial hypertrophy after treatment with 147 mg/kg/day of dibromochloromethane. Histological evaluation of the liver indicated several effects. There was a dose-related increase in centrilobular pallor and focal inflammation after treatment with bromodichloromethane at the mid- (74 mg/kg/day) as well as the high- (148 mg/kg/day) dose level and an increased number of mitotic figures present after treatment with 74 mg/kg/day of bromodichloromethane, but not at the other dose levels. There was also a dose-related increase in the number of mitotic figures (0, 0, 11, 31 for controls, low-, medium- and high-dose, respectively) and increased cytoplasmic vacuolization (1, 21, 4, 35 for control, low-, medium- and high-dose, respectively) after treatment with

dibromochloromethane. The increase in hepatocytic vacuolization may be due to fatty infiltration, especially if the slides were routinely prepared with the use of lipid-solvents such as xylene. Vacuolization of hepatocytes was reported in 3 of 5 mice treated with 37 mg/kg/day, 4 of 10 mice treated with 74 mg/kg/day, and 8 of 10 mice treated with 147 mg/kg/day of dibromochloromethane.

5.5.2. **Bromochloromethane.** Groups of 20 male and 20 female rats, 10 male and 10 female guinea pigs, two male and two female rabbits and 10 female mice were exposed by inhalation to 0, 500 or 1000 ppm of bromochloromethane for 7 hours/day, 5 days/week for 4-6 months (Torkelson et al., 1960). In addition, a group of 10 female rats and one male and one female dog were exposed to 370 ppm of bromochloromethane for 7 hours/day, 5 days/week for 4-6 months. At an exposure level of 500 and 1000 ppm, both male and female rats had normal body weights and increased relative liver and kidney weights. Hepatic histopathology, including cloudy swelling and vacuolization of hepatocytes was reported at the higher exposure level (1000 ppm) for males and females. At an exposure of 500 ppm only the females displayed liver histopathology that consisted of bile duct epithelial proliferation and portal fibrosis. The female rats exposed to 370 ppm of bromochloromethane had increased relative liver weights, but no other gross or microscopic pathology. Torkelson et al. (1960) ascribed the increased liver weight to stress. Blood bromide levels were elevated in both sexes at exposure levels of 1000 and 500 ppm and in the females at 370 ppm. At an exposure level of 1000 ppm of bromochloromethane, female guinea pigs had an increased number of presumably circulating neutrophils as well as decreased body weight and increased relative liver and kidney weights; male guinea pigs had decreased body weight coupled with increased relative weight of

both the liver and kidney, as well as decreased spermatogenesis. At 500 ppm, the body weight of male and female guinea pigs were depressed, the relative liver weights were increased, and the relative kidney weight in the males was increased. The only effect seen in the rabbits was decreased spermatogenesis in one of the two males exposed to 1000 ppm of bromochloromethane. The only responses reported in groups of 10 female mice exposed to 1000 or 500 ppm of bromochloromethane for 7 hours/day, 5 days/week for 7 weeks were increased relative liver and kidney weights as well as decreased body weight. No effects were reported in the dogs (Torkelson et al., 1960).

Pertinent data regarding the chronic or subchronic toxicity of bromotrichloromethane, tribromochloromethane or dibromodichloromethane were not located in the available literature cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

The acute oral LD_{50} values of bromodichloromethane and dibromochloromethane in rats observed for 14 days were reported by Chu et al. (1982b). For bromodichloromethane, the values and the 95% confidence limits were 916 (779-1083) mg/kg for male rats and 969 (764-1198) mg/kg for female rats and for dibromochloromethane were 1186 (997-1421) mg/kg for male rats and 848 (576-1090) mg/kg for female rats. The acute oral LD_{50} values for these chemicals in mice observed for 14 days were reported by Bowman et al. (1978). For bromodichloromethane the LD_{50} was 450 (326-621) mg/kg for male mice and 900 (811-999) mg/kg for female mice, and for dibromochloromethane the LD_{50} was 800 (667-960) mg/kg for male mice and 1200 (945-1524) mg/kg for female mice.

The acute toxicity studies in mice and rats (Bowman et al., 1978; Chu et al., 1980, 1982a) indicate that the liver, along with the kidneys, and perhaps the adrenals, lungs and brain, are the major targets of halomethane

poisoning. Sedation, followed by ataxia, flaccid muscle tone, anesthesia and narcosis, are the usual effects of bromodichloromethane and dibromochloromethane exposure (Bowman et al., 1978; Chu et al., 1980, 1982a).

Groups of 20 male rats 6-8 weeks of age exposed for 15 minutes to 360, 500, 590, 600, 690, 720, 850, 900, 1200, 1799 or 2025 ppm of bromotrichloromethane by inhalation had mortality rates of 0/20, 7/20, 15/20, 9/20, 10/20, 4/20, 16/20, 17/20, 19/20, 20/20 and 19/20, respectively (Haun et al., 1969). Although the rats were observed for 14 days after exposure to bromotrichloromethane, all of the deaths occurred within the first 2 days. Haun et al. (1969) reported that the LC_{50} was 465 ppm with a range of 424-511 ppm at the 95% confidence level.

Inhalation by rats of an unspecified dose of bromotrichloromethane, resulted in liver steatosis, possibly as a consequence of free-radical formation (Calligaro et al., 1971). Several biochemical effects of treatment with bromotrichloromethane included an altered cGMP/cAMP ratio (Paradisi et al., 1984), an increased calcium concentration (Paradisi et al., 1984; Lowrey et al., 1981; Recknagel et al., 1981; Waller et al., 1983) swelling of the endoplasmic reticulum in hepatocytes (Calligaro et al., 1971; Bini et al., 1978), hepatic polysome breakdown (Calligaro et al., 1971; Bini et al., 1978), decreased levels of glucose-6-phosphatase (Calligaro et al., 1971), increased hepatic membrane lipid peroxidation (Calligaro et al., 1971; Ugazio et al., 1973; Benedetti et al., 1982a,b; Recknagel et al., 1981; Waller et al., 1983; Koch et al., 1974; Lowrey et al., 1981), but no decrease in the polysomal profile of rat brain homogenate (Corongiu et al., 1973). The combined results of the above experiment indicate that the metabolism of bromotrichloromethane by cytochrome P-450 resulted in peroxidation of the membrane lipids of hepatocytes, particularly in the endoplasmic reticulum, which is recovered as the microsomal fraction upon

differential centrifugation of the homogenate of these cells. Release of calcium sequestered in the endoplasmic reticulum membrane was one of the earliest effects of membrane lipid peroxidation reported. The lipid peroxidation that occurred in the membranes of hepatocytes after bromotrichloromethane treatment may at least partially account for the subsequent hepatic histopathology, such as steatosis and necrosis.

Radioactively labelled bromotrichloromethane has been reported to bind covalently to calf thymus DNA after bioactivation by hepatic microsomes (DiRenzo et al., 1982).

The hepatotoxicity of bromotrichloromethane was altered by pretreatment with various chemicals. Intraperitoneal injection of male rats with ~18 mg/100 g/bw of phenobarbital 48 hours before oral poisoning with bromotrichloromethane at lethal doses increased the amount of fatty infiltration observed in the liver; whereas, intraperitoneal injection of male rats with SKF-525A (5 mg/100 g/bw), a mixed function oxidase inhibitor, 45 minutes before oral poisoning with bromotrichloromethane (5 mL/kg) or intraperitoneal injection of male rats with DPPD (600 mg/kg), a mixed function oxidase inhibitor and antioxidant, 48 and 24 hours before oral poisoning with bromotrichloromethane, decreased the amount of fatty infiltration observed in the liver (Torrielli et al., 1974). Torielli et al., (1974) further reported that SKF-525A protected against fatty infiltration in the liver only if the bromotrichloromethane was administered orally. Inhalation of bromotrichloromethane after SKF-525A administration resulted in fatty infiltration of the liver. Koch (1975) reported that low levels of liver microsomal cytochrome P-450 protected rats against lethal doses of bromotrichloromethine. Pretreatment of rats with small doses of bromotrichloromethane followed by lethal doses of bromotrichloromethane, however, did not protect

the rats from the effects of the lethal dose of bromotrichloromethane, suggesting an extrahepatic site of action for bromotrichloromethane (Koch et al., 1974).

Pretreatment of male Sprague-Dawley rats with 225 ppm of phenobarbital for 15 days followed by an intraperitoneal injection of 10 µℓ/kg of bromotrichloromethane or 10 µℓ/kg of tribromochloromethane did not result in hepatic histopathology; however, pretreatment of male rats with 10 ppm of chlordecone (Kepone) for 15 days followed by an intraperitoneal injection of 10 µℓ/kg of bromotrichloromethane or 10 µℓ/kg of tribromochloromethane resulted in pronounced liver centrilobular necrosis and levels of SGPT and SGOT three times higher than the level produced by bromotrichloromethane administration alone (Klingensmith and Mehendale, 1981). Agarwal and Mehendale (1982a,b) reported additional experiments that confirmed the potentiating effect of chlordecone pretreatment on bromotrichloromethane administration.

Cardiac effects have been described after treatment with bromochloromethane. A group of seven dogs that had been anesthetized with morphine (4 mg/kg), atropin sulfate (0.2 mg/kg), subcutaneously and α-chloralose (70 mg/kg), intravenously, responded to an ~2 hour exposure of 0.3-1.0% bromochloromethane in oxygen by a decrease in venous pyruvate content and by a moderate decrease in coronary blood flow accompanied by an increase in coronary venous oxygen pressure and oxygen content (Van Stee, 1974; Van Stee et al., 1975). Terpolilli et al. (1979) reported in an abstract that urethane anesthetized guinea pigs exposed to 3.5% bromochloromethane in the air for 30 minutes, had decreased cardiac contractility as well as an increased heart rate and elevated blood pressure.

Acute accidental human exposure to bromochloromethane resulted in gastrointestinal disturbances as well as CNS narcosis. The patients recovered with supportive therapy, in particular with the application of artificial respiration during apnea (Rutstein, 1963).

Dibromochloromethane and dibromodichloromethane have been identified in samples of human milk collected in New Jersey (Bayonne and Jersey City), Pennsylvannia (Bridgeville) and Louisianna (Baton Rouge) (Pellizzari et al., 1982). Halomethane consumption by infants may be increased by the use of cleaning solutions for baby bottles as well as by using tap water, as opposed to boiled water, in the preparation of infant formulas and foods (Lahl et al., 1982).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Pertinent data regarding acute toxic effects of any bromochloromethanes to aquatic animals were not located in the available literature cited in the Appendix.

6.2. CHRONIC TOXICITY

The effects of bromodichloromethane and dibromochloromethane on the survival and development of common carp (Cyprinus carpio) embryos was studied by Trabalka et al. (1980) and Mattice et al. (1981). Carp embryos were exposed to the toxicant from fertilization until hatching (4-5 days) and survival until hatching was used to determine LC_{50} values. Toxicant solutions were renewed every 8 hours, which is due to a decline in toxicant concentration. The LC_{50} values for carp embryos exposed to bromodichloromethane and dibromochloromethane were 119 and 53 mg/ℓ (initial concentration) (Trabalka et al., 1980). After correcting for toxicant loss, the LC_{50} values were reported to be 67.4 and 33.5 mg/ℓ, respectively (Mattice et al., 1981).

6.3. PLANT EFFECTS

Pertinent data regarding effects of the bromochloromethanes on aquatic plants were not located in the available literature cited in the Appendix.

6.4. RESIDUES

Trabalka et al. (1980) reported the half-lives of bromochloromethane and dibromochloromethane in freshwater were 4.4 and 5.6 hours, respectively. Kasso and Wells (1981) conducted analyses on drinking water samples from Murfreesboro, Tennessee and detected levels of bromodichloromethane and dibromochloromethane of 5.0-11.9 and 1.4-5.3 µg/ℓ, respectively. Hiatt

(1983) reported detecting bromochloromethane in tissue from rainbow trout collected from the Colorado River. The estimated concentration in the whole-fish sample was 8 µg/ℓ.

6.5. OTHER RELEVANT INFORMATION

Additional data associated with the toxicity of the bromochloromethanes to aquatic organisms were not located in the available literature cited in the appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Based on the animal data of MacEwen et al. (1966), Torkelson et al. (1960) and Highman et al. (1948) and on the carboxyhemoglobin formation in exposed individuals, the ACGIH (1980, 1983) has recommended a TWA-TLV of 200 ppm (~1050 mg/m³), with a STEL of 250 ppm (~1300 mg/m³) for bromochloromethane. OSHA has established a standard for occupational bromochloromethane exposure of 200 ppm (1050 mg/m³) for an 8-hour TWA (CFR, 1981). A human ADI of 0.039 mg/day for bromodichloromethane and of 0.036 mg/day for dibromochloromethane was reported by the U.S. EPA (1982). The ADIs were based on a NOAEL of 5 ppm of either chemical in the drinking water of rats for 90 days. At higher concentrations, increased severity of liver lesions occurred.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of bromochloromethanes were not located in the available literature cited in the Appendix.

B. RISK ASSESSMENT

The carcinogenicity of the bromochloromethanes has not been adequately studied. The bromodichloromethane study by Theiss et al. (1977) on male mice revealed no significant increased incidence of lung tumors after 18-24 intraperitoneal injections of bromodichloromethane at ≤100 mg/injection for 6-8 weeks and a recovery of 18 weeks.

Epidemiologic studies (Isacson et al., 1983; Aldrich and Peoples, 1982) have correlated increased incidences of human cancer (bladder cancer for males; rectal cancer for males and females; and malignant melanoma) with increased concentrations of bromodichloromethane and dibromochloromethane in drinking water; however, such studies are of limited adequacy for use in quantitative risk assessment (see Table 5-1).

Bromochloromethane, bromodichloromethane and dibromochloromethane, the only halomethanes on which mutagenicity testing was reported, were mutagenic in Salmonella typhimurium (Simmon, 1978; Simmon et al., 1977; Simmon and Tardiff, 1978; Osterman-Golkar et al., 1983) without metabolic activation. Bromochloromethane was also mutagenic to Escherichia coli in the absence of metabolic activation (Osterman-Golkar et al., 1983). Bromodichloromethane and dibromochloromethane increased the incidence of sister chromatid exchange in mouse bone marrow and in cultivated human lymphocytes (Morimoto and Koizumi, 1983). Dibromochloromethane was negative in a dominant lethal assay in mice (Borzelleca and Carchman, 1982).

Treatment of pregnant rats with bromodichloromethane on days 6-15 of gestation caused slight maternal toxicity at all dose levels (50, 100 or 200 mg/kg/day), as evidenced by increased relative liver weight, and fetotoxicity at the highest dose (200 mg/kg/day) tested; fetotoxicity was indicated

by altered patterns of ossification (Ruddick et al., 1983). As reported in the same study (Ruddick et al., 1983), dibromochloromethane was maternotoxic only at the highest dose tested (200 mg/kg/day), as evidenced by decreased maternal weight gain, and did not appear to cause any fetotoxicity. Neither bromodichloromethane nor dibromochloromethane appeared to be teratogenic in the Ruddick et al. (1983) study. No teratogenic effects of dibromochloromethane at concentrations in the drinking water of $\leq$4 mg/mℓ were observed in mice (Borzelleca and Carchman, 1982).

The dibromochloromethane two-generation reproductive study in mice (Borzelleca and Carchman, 1982) indicated that at the lowest dose tested (0.1 mg/mℓ or 100 ppm, which is equivalent to 17 mg/kg/day assuming a mouse consumes 0.17 ℓ/kg bw/day) the body weight of the newborn pups in the F_{2b} generation was significantly depressed and remained depressed throughout the lactation period. At the next highest dose tested (1 mg/mℓ or 1000 ppm, which is equivalent to 170 mg/kg/day assuming a mouse consumes 0.17 ℓ/kg bw/day), there was a decrease in female body weight and an increase in the occurrence of liver histopathology, in addition to significant decreases in litter size, pup viability, postnatal body weight and the lactation index. At the highest dose tested (4 mg/mℓ or 4000 ppm, which is equivalent to 680 mg/kg/day), the effects were the same type but more severe.

Although no lifetime studies of exposure to bromochloromethanes were available, several oral 90-day studies have been conducted in rats and mice using bromodichloromethane and dibromochloromethane (Chu et al., 1982a,b; Balster and Borzelleca, 1982; Schuller et al., 1978; Munson et al., 1978) and an inhalation study of 4-6 months duration was conducted in guinea pigs, rabbits, rats and mice using bromochloromethane (Torkelson et al., 1960).

Relatively high gavage dosages of bromodichloromethane and dibromochloromethane (100 and 400 mg/kg/day) for 60-90 days resulted in high mortality in mice as well as significant alteration of operant behavior (Balster and Borzelleca, 1982). No effects on behavioral indices were observed at the lower dosages ($\leq$11.6 mg/kg/day). Dose-related suppressions of hepatic phagocytosis in mice were reported for bromodichloromethane and dibromochloromethane at daily gavage dosages of 0.3, 12.5 or 125 mg/kg/day for 90 days (Munson et al., 1978). Suppression of splenic phagocytosis was dose-related at $\geq$12.5 mg/kg/day of dibromochloromethane. Delayed hypersensitivity was depressed in mice treated by gavage with bromodichloromethane at 125 mg/kg/day for 90 days (Schuller et al., 1978). These studies of Munson et al. (1978) and Schuller et al. (1978) were reported only in abstract form; hence, numbers of animals were not specified and dose-response data were not clear.

The subchronic (90 days of treatment, plus 90 days of recovery) study of Chu et al. (1982b) reported histological alterations in the liver and thyroid after exposure to bromodichloromethane and dibromochloromethane in the drinking water, as well as a decreased lymphocyte count in females exposed to the highest concentration of bromodichloromethane (2500 ppm). No hematologic or biochemical changes, such as serum enzyme levels, were reported at any concentration level (5, 50, 500 or 2500 ppm) with either chemical. The histologic changes reported in the thyroid gland (reduced follicle size and increased epithelial height), which were not dose-related, cannot be interpreted meaningfully in the absence of additional data, such as circulating thyroxine levels; however, fatty infiltration of hepatocytes can be correlated with the hepatotoxicity of a xenobiotic. An increased incidence of hepatic histopathology was reported at all levels (5, 50, 500

and 2500 ppm) for males and females treated with bromodichloromethane and dibromochloromethane; however, the level of statistical significance was not reported. The severity of the hepatic lesions was significantly increased at the highest dose level for both halomethanes in males and females and at a concentration of 50 ppm for males and females treated with bromodichloromethane and for the females treated with dibromochloromethane. The lowest concentration (5 ppm) tested of bromodichloromethane or dibromochloromethane did not elicit a significant increase in the severity of the hepatic histopathology in either males or females. Therefore, the U.S. EPA (1982) designated 5 ppm (0.14 mg/rat/day for the males and 0.13 mg/rat/day for the females) of bromodichloromethane and 5 ppm (0.14 mg/rat/day for the males and 0.11 mg/rat/day for the females) of dibromochloromethane as a NOAEL. Equivalent dosages in mg/kg/day are presented in Table 8-1. The NOAELs are well below the doses used in the rat teratology study (Ruddick et al., 1983) where the lowest dose tested (50 mg/kg/day) of bromodichloromethane resulted in an increase in the relative maternal liver weight. The NOAELs are also lower than doses used in the mouse 2-generation reproductive study (Borzelleca and Carchman, 1982) where the lowest dose tested (17 mg/kg/day, derived from an experimental dose of 0.1 mg/mℓ in the drinking water with the assumption that a mouse consumes 0.17 ℓ/kg body weight/day) of dibromochloromethane resulted in decreased birth weight and decreased weaning weight in the F_{2b} generation.

The information that the U.S. EPA (1982) used to calculate the doses (see Table 8-1) was obtained in a personal communication from Dr. Chu to Dr. Dourson (Chu, 1982). The U.S. EPA (1982) averaged the bromodichloromethane dose for the male (0.45 mg/kg/day) and female (0.67 mg/kg/day) rats to obtain an animal NOAEL of 0.56 mg/kg/day of bromodichloromethane. The human

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TABLE B-1

Dose Calculations for Rats Given Trihalomethanes Via Drinking Water[a]

Chemical and Concentration[b]	Male			Female		
	mg/rat/day	avg. wt. in kg[c]	mg/kg/day[d]	mg/rat/day	avg. wt. in kg[c]	mg/kg/day[d]
Dibromochloromethane						
5	0.14	0.317	0.442	0.11	0.188	0.585
50	1.5	0.304	4.93	1.2	0.187	6.42
500	12	0.304	39.5	9.5	0.192	49.5
2500	55	0.272	202	38	0.180	211
Bromodichloromethane						
5	0.14	0.311	0.450	0.13	0.194	0.670
50	1.6	0.308	5.20	1.2	0.181	6.63
500	13	0.302	43.1	9.8	0.184	53.3
2500	49	0.260	189	32	0.160	200

[a]Source: U.S. EPA, 1982

[b]ppm in drinking water

[c]Data obtained from Chu et al., 1982b

[d]Doses were calculated on average body weights during exposure of animals sacrificed at 90 days; approximately 10 animals/group.

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ADI of 0.039 mg/day was obtained by multiplying the animal NOAEL by the assumed weight of a man (70 kg) and dividing by an uncertainty factor of 1000 to account for interspecies extrapolation (10), the range of sensitivity to xenobiotics within the human population (10) and the use of a subchronic study to calculate a human ADI (10).

In a similar way, the U.S. EPA (1982) averaged the dibromochloromethane dose for the male (0.44 mg/kg/day) and for the female (0.59 mg/kg/day) rats to obtain an animal NOAEL of 0.515 mg/kg/day of dibromochloromethane. The human ADI for dibromochloromethane of 0.036 mg/day was obtained by multiplying the animal NOAEL by the assumed weight of a man (70 kg) and dividing by an uncertainty factor of 1000 to account for interspecies extrapolation (10), the range of sensitivity to xenobiotics within the human population (10), and the use of a subchronic study to calculate a human ADI (10).

After exposing groups of 20 male and 20 female rats, 10 male and 10 female guinea pigs and 10 female mice by inhalation to 0, 500 or 1000 ppm of bromochloromethane, as well as one group of 10 female rats to 370 ppm of bromochloromethane, for 7 hours/day, 5 days/week for 4-6 months, Torkelson et al. (1960) reported that there were statistically significant changes in mouse and guinea pig body weights and relative liver and kidney weights at exposure levels of 500 and 1000 ppm of bromochloromethane. In addition, there were statistically significant differences in relative liver weights in male and female rats exposed to 500 or 1000 ppm of bromochloromethane that were accompanied by histopathological changes such as cloudy swelling, vacuolization in males and females exposed to 1000 ppm and vacuolization and fibrosis in the females exposed to 500 ppm of bromochloromethane. The female rats exposed to 370 ppm of bromochloromethane had increased relative liver weights without the accompanying histopathology. Since this study is

subchronic, did not clearly define a NOAEL, and only employed female rats as test animals at the lowest dose tested, it is deemed inadequate for quantitative risk assessment.

Data were insufficient for deriving ADIs for bromotrichloromethane, dibromodichloromethane and tribromochloromethane.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The toxic effects of bromodichloromethane, dibromochloromethane and bromochloromethane are sufficiently different to warrant separate RQ determinations. Data are not sufficient for deriving RQs for bromotrichloromethane, dibromodichloromethane and tribromochloromethane.

9.1.1. Derivation of the RQ for Bromodichloromethane. The toxic effects of bromodichloromethane exposure were presented in Chapter 5. No studies of a chronic nature were available, but 60- and 90-day studies in mice and a 90-day study in rats as well as a teratogenicity study in rats described effects. Bromodichloromethane has been reported to cause delayed fetal ossification in rats whose dams ingested 200 mg/kg/day, and dose-related increased incidences of sternabrae abnormalities in rats whose dams ingested ≥50 mg/kg/day on days 6-15 of gestation (Ruddick et al., 1983); the dams had increased liver weight at ≥50 mg/kg/day and decreased body weight gain and increased kidney and brain weights at 200 mg/kg/day. Rats treated with bromodichloromethane in drinking water at 2500 ppm for 90 days had decreased body weight gain and alterations in the number of circulating lymphocytes (Chu et al., 1982b). The severity of liver lesions were significantly greater at ≥50 ppm in the drinking water (Chu et al., 1982b). Mice ingesting 100 mg/kg/day for 60 days (Balster and Borzelleca, 1982) had increased mortality and decreased operant behavior. Mice receiving gavage doses of bromodichloromethane of 125 mg/kg/day for 90 days had inhibition of delayed hypersensitivity and suppressed humoral immunity (Schuller et al., 1978). In a similar study, mice had a dose-related suppression of hepatic phagocytosis at ≤125 mg/kg/day, but the threshold was not defined (Munson et al.,

1978). The data on the effects of subchronic and in utero exposure to bromodichloromethane used to calculate CSs are presented in Table 9-1. The human MED in units of mg/day was derived from the animal dose by multiplying the animal dose in units of mg/kg/day by the cube root of the ratio of animal to human (assumed to be 70 kg) body weight and subsequently multiplying by 70 kg. In the study by Chu et al. (1982b), the animal body weights presented in Table 8-1 were used; for the Ruddick et al. (1983) study, the rat weight was assumed to be 0.35 kg, and for the mouse studies, the weight was assumed to be 0.03 kg. If the study was subchronic, the animal dose in mg/kg/day was divided by 10 before deriving the human MED.

The doses in mg/kg/day from the concentrations in drinking waters were calculated by U.S. EPA (1982) from the data of Chu et al. (1982b) and from a personal communication from Dr. Chu to Dr. Dourson (Chu, 1982) (see Chapter 8 and Table 8-1). The doses corresponding to 50 ppm bromodichloromethane are 5.2 mg/kg/day for males and 6.63 mg/kg/day for females. Increased severity of liver lesions were observed at $\geq$5.2 mg/kg/day, which is equal to a human MED of 6.0 mg/day and corresponds to an RV_d of 4.3. The liver lesions were described as mild to moderately severe and included fatty infiltration, vesiculation of biliary epithelial nuclei and hyperplasia. These effects are assigned an RV_e of 5 and the resultant CS ($RV_d \times RV_e$) is 21.5, corresponding to an RQ of 100.

At 2500 ppm (corresponding to 189 mg/kg day for males and 200 mg/kg/day for females) there was decreased body weight gain. The human MED corresponding to 189 mg/kg/day is 205 mg/day, and the RV_d is 2.0. Decreased body weight gain has an RV_e of 4, the CS is 8 and the RQ is 1000. At 2500 ppm (200 mg/kg/day), female rats had decreased lymphocyte counts (RV_e=4). The human MED is 184 mg/day, the RV_d is 2.1, the CS is 8.4 and the RQ is

TABLE 9-1

Composite Scores for Systemic Toxicity of Bromodichloromethane

ecies	Animal Dose (mg/kg/day)	Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
at	50 on days 6-15 of gestation	598	1.3	Fetotoxicity as indicated by increased incidence of sternebrae abnormalities.	8	10.4	1000	Ruddick et al., 1983
Rat	189 for 90 days	205*	2.0	Decreased body weight	4	8	1000	Chu et al., 1982b
Rat	200 for 90 days	184*	2.1	Decreased number of lymphocytes	4	8.4	1000	Chu et al., 1982b
Rat	5.2 for 90 days	6.0*	4.3	Increased severity of liver lesions, including fatty changes in the livers of female rats	5	21.5	100	Chu et al., 1982b
Mouse	125 for 90 days	66.0*	2.8	Suppression of humoral immunity and delayed hypersensitivity	6	16.8	1000	Schuller et al., 1978

*The human MED was divided by an uncertainty factor of 10 to approximate chronic exposure.

In the teratogenicity study, there was delayed ossification in the offspring of dams treated at 200 mg/kg/day and there was a dose-related increased incidence of sternebrae abnormalities at ≥50 mg/kg/day. The dose of 50 mg/kg/day corresponds to a human MED of 598 mg/day, which has an RV_d of 1.3. The RV_e for fetotoxic effects is 8. Therefore, the CS is 10.4, corresponding to an RQ of 1000.

In the 90-day gavage study in mice, the dosage of 125 mg/kg/day corresponds to an MED of 66 mg/day, which has an RV_d of 2.8. Impaired immune function, as evidenced by suppressed humoral immunity and delayed hypersensitivity, was given an RV_e of 6. The resulting CS is 16.8 and corresponds to an RQ of 1000.

Since the effect of increased severity of liver lesions at ≥5.2 mg/kg/day results in the highest CS, the RQ of 100 is recommended for bromodichloromethane (Table 9-2).

9.1.2. Derivation of the RQ for Dibromochloromethane. The toxic effects of dibromochloromethane exposure are presented in Chapter 5. No studies of a chronic nature were available, but 60- and 90-day studies in mice, a 90-day study in rats, teratology studies in rats and mice, and a reproduction study in mice have been conducted.

Mice treated by gavage for 90 days with dibromochloromethane had suppression of hepatic and splenic phagocytosis at 12.5 and 125 mg/kg/day (Munson et al., 1978).

In a 2-generation reproduction study in mice, adult mice of the F_0 and F_{1b} generations had increasing severity and incidence of gross liver lesions (Borzelleca and Carchman, 1982). At 0.1 mg/mℓ in the drinking water, the lesions consisted of a yellow-gray color presumed to be due to fat accumulation. At 1.0 mg/mℓ, the lesions varied in severity from

TABLE 9-2

Bromodichloromethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	6.0 mg/day
Effect:	increased severity of liver lesions, including fatty changes in the livers of rats
Reference:	Chu et al., 1982b
RV_d:	4.3
RV_e:	5.0
Composite Score:	21.5
RQ:	100

*Equivalent human dose

yellow color to distinct masses on the surface. At 4.0 mg/mL, large nodules were present on and within the liver surface. Parental body weights were also significantly decreased at 1.0 and 4.0 mg/mL. Fetotoxicity was evidenced by decreased postnatal body weight of F_{2b} mice at 0.1 mg/mL and decreased postnatal body weight, litter size and pup viability at 1.0 and 4.0 mg/mL. Lactation and gestation indices were also decreased at 1.0 and 4.0 mg/mL. No teratogenic effects were observed.

No teratogenic or fetotoxic effects were observed in the offspring of rats treated by gavage with dibromochloromethane at 50, 100 or 200 mg/kg/day during days 6-15 of gestation (Ruddick et al., 1983).

Rats treated with dibromochloromethanes in the drinking water for 90 days had significantly increased severity of liver lesions, which were characterized as fatty infiltration and hyperplasia of the biliary epithelium. Increased severity of liver lesions was observed at a concentration of $\geq$50 ppm (Chu et al., 1982b).

The data used to calculate CSs are presented in Table 9-3. The human MED values in units of mg/day were derived from the animal dosages as described previously (see Section 9.1.1.).

In the 2-generation study (Borzelleca and Carchman, 1982), mice were exposed to dibromochloromethane in the drinking water at 0.1, 1.0 and 4.0 mg/mL (100, 1000 or 4000 ppm). Assuming that a mouse imbibes an amount of water equal to 17% of its body weight, the dosages in mg/kg/day that were used to calculate MEDs were 17 and 170 mg/kg/day, which correspond to MEDs of 89.7 and 897 mg/day, respectively, and RV_ds of 2.6 and 1.1, respectively. The effects at 17 mg/kg/day included fat accumulation in livers of parental mice (RV_e=5) and evidence of fetotoxicity (RV_e=8). The CS using the parental data is 13.0, corresponding to an RQ of 1000; the CS

TABLE 9-3

Composite Scores for Systemic Toxicity of Dibromochloromethane

Species	Animal Dose (mg/kg/day)	Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Mouse	17 (2-generation study)	89.7	2.6	Increased incidence of gross liver changes (fat accumulation)	5	13.0	1000	Borzelleca and Carchman, 1982
Mouse	170 (2-generation study)	897	1.1	Increased incidence and severity of liver lesions (distinct masses on surface)	6	6.6	1000	Borzelleca and Carchman, 1982
Mouse	17 (2-generation reproductive study)	89.7	2.6	Fetotoxicity as indicated by decreased body weight in the F_{2b} generation at birth and at 3 weeks of age	8	20.8	100	Borzelleca et al., 1982
Mouse	12.5 for 90 days	6.6[a]	4.3	Suppression of hepatic and splenic phagocytosis	6	25.8	100	Munson et al., 1978
Rat	6.42 for 90 days	6.2[a]	4.3	Increased severity of liver lesions including fatty changes in female livers	5	21.5	100	Chu et al., 1982b

[a]In the derivation of the human MED, the animal in mg/kg/day was divided by an uncertainty factor of 10 because these were all subchronic studies.

using the offspring data is 20.8, corresponding to an RQ of 100. At 170 mg/kg, distinct masses were observed on the surface of the liver; histologic examination was not performed, but an RV_e of 6 seems appropriate. The resultant CS of 6.6 corresponds to an RQ of 1000.

The study by Munson et al. (1978) reported impairment of the immune system, as evidenced by suppression of hepatic and splenic phagocytosis (RV_e=6) at 12.5 mg/kg/day, which results in an MED of 6.6 mg/day and an RV_d of 4.3. The product of the RV_d and the RV_e equals a CS of 25.8, corresponding to an RQ of 100. In the study of Chu et al. (1982b), rats treated at 6.42 mg/kg/day (MED=6.2 mg/day; RV_d=4.3) had fatty changes in the liver (RV_e=5). The CS is 21.5, corresponding to an RQ of 100.

In a previous determination of the RQ for dibromochloromethane (U.S. EPA, 1983), the data from the 90-day study in mice by Munson et al. (1978) was used as the basis for the RQ; the 2-generation study (Borzelleca and Carchman, 1982) and the 90-day study in rats (Chu et al., 1982a,b) were not available at the time of the previous determination. Nevertheless, the data of Munson et al. (1978) still provide the highest CS, while the data from the other studies support the choice of the Munson et al. (1978) as the basis of the RQ (Table 9-4).

9.1.3. Derivation of the RQ for Bromochloromethane. The Torkelson et al. (1960) study, which is the only animal study located in the available literature on the systemic effects of bromochloromethane, evaluated the effects of subchronic inhalation exposure (4-6 months) to bromochloromethane in rats, mice, guinea pigs, dogs and rabbits. No effects were observed in dogs exposed at 370 ppm; the only effect in rabbits was decreased spermatogenesis in one of the two males. There were histologic indications of decreased spermatogenesis in the guinea pig at 1000 ppm, but no functional

TABLE 9-4

Dibromochloromethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	6.6 mg/day
Effect:	suppression of hepatic and splenic phagocytosis
Reference:	Munson et al., 1978
RV_d:	4.3
RV_e:	6
Composite Score:	25.8
RQ:	100

*Equivalent human dose

evaluation of spermatogenesis was reported. Guinea pigs also had increased numbers of circulating neutrophils at 1000 ppm. Body weights were decreased in mice and guinea pigs at ≥500 ppm, relative liver weights were increased in rats at ≥370 ppm, and relative liver and kidney weights were increased in rats, guinea pigs and mice at ≥500 ppm. Rats had histopathologic liver lesions consisting of bile duct epithelial proliferation and portal fibrosis at 500 ppm and cloudy swelling and vacuolization of hepatocytes at 1000 ppm. The animal exposures in ppm were converted to units of mg/m³ by multiplying by the molecular weight of bromochloromethane (129.39) and dividing by 24.45. By multiplying the exposure level in mg/m³ by 7/24 hours and 5/7 days (to convert it to continuous exposure) and subsequently multiplying by the animal breathing rate, dividing by the animal body weight and multiplying by $\sqrt[3]{\text{animal body weight} \div \text{human body weight}}$ and multiplying by a human body weight of 70 kg, the equivalent human MED is obtained. Because the Torkelson et al. (1960) study was subchronic, the human MEDs were divided by 10. Table 9-5 summarizes the data used to calculate CSs.

All of the CSs corresponded to RQs of 1000. As seen from Table 9-5, the highest CS is obtained using the data for decreased spermatogenesis in guinea pigs and is used as the basis for the RQ (Table 9-6).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The available data on the carcinogenicity of the bromochloromethanes was presented in Section 5.1. and Table 5-1. IARC (1982) does not list any of the bromochloromethanes. Although levels of bromodichloromethane and dibromochloromethane in drinking water were correlated with an increased incidence of human cancer (melanoma, bladder cancer, lung cancer, rectal cancer, breast cancer and stomach cancer) in Iowa (Isacson et al., 1983) and Florida (Aldrich and Peoples, 1982) (see Table 5-1), the incidences were

TABLE 9-5

Composite Scores for Systemic Toxicity of Bromochloromethane[a]

Species	Animal Exposure[b]	Human MED[c] (mg/day)	RV_d	Effects	RV_e	CS	RQ
Guinea pigs	5292 (1000 ppm)	279.4	1.8	Microscopic decreased spermatogenesis of tubules with fibrosis; increased numbers of circulating neutorphils, increased relative liver and kidney weight	6	6	1000
Guinea pig	2646 (500 ppm)	139.7	2.3	Decreased body weight, increased relative liver and kidney weight	4	5.6	1000
Mouse	2646 (500 ppm)	385.9	1.6	Decreased body weight, increased relative liver and kidney weight	4	6.5	1000
Rat	1958 (370 ppm)	312.5	1.8	Increased relative liver weight	4	6.4	1000
Rat	2646 (500 ppm)	422	1.6	Microscopic liver lesions: bile duct epithelial proliferation and portal fibrosis with increased liver and kidney weights	4	5.6	1000
Rat	5292 (1000 ppm)	844	1.1	Microscopic liver lesions: cloudy swelling and vacuolization of hepatocytes, increased liver and kidney weights	5	5	5000

[a]Source: Torkelson et al., 1960

[b]Exposures were for 7 hours/day, 5 days/week for 4-6 months.

[c]The MEDs were divided by 10 to approximate chronic exposure.

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TABLE 9-6

Bromochloromethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	408 mg/day
Effect:	increased relative liver weight
Reference:	Torkelson et al., 1960
RV_d:	1.6
RV_e:	4
Composite Score:	6.4
RQ:	1000

*Equivalent human dose

also highly correlated with the concentration of chloroform, which was higher than either of the bromochloromethanes. Therefore, the data for carcinogenic potential of bromochloromethane in humans is insufficient. The only completed animal study on the carcinogenicity of bromodichloromethane (Theiss et al., 1977) indicated no significant increased incidence of lung tumors in mice intraperitoneally injected with 20, 40 or 100 mg/kg of bromodichloromethane 3 times/week for 6 weeks and observed for an additional 18 weeks. A carcinogenesis bioassay in rats and mice treated by gavage with bromodichloromethane is currently being conducted by the NTP (Powers, 1980; NTP, 1984); however, at the present time, there is insufficient animal data available from which to derive a potency factor ($1/ED_{10}$). Therefore, the bromochloromethanes, according to current EPA guidelines, would be placed in group D; that is, data are inadequate to judge the carcinogenic potential of this group of compounds.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory 1967-1978. USDI, Fish and Wildlife Service Resource Publ. 137., Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. NTIS PB-269605.

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